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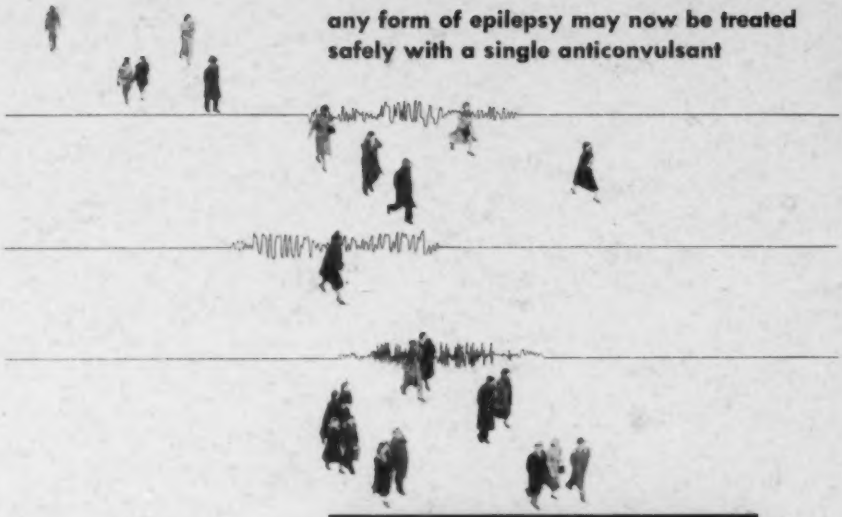

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Original Communications

PERTUSSIS: CLINICAL COMPARISON OF THE NEWER ANTIBIOTICS

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PROVIDENCE, R. I.

PERTUSSIS has long been known for its remarkable resistance to preventive as well as therapeutic efforts. A number of reports of in vitro studies[1, 2, 3, 4, 5, 6] have appeared in the pediatric literature recently which have suggested the efficacy of several antibiotic agents against the *Hemophilus pertussis* organism. Unfortunately, however, as with many experimental therapeutic drugs, the most effective agents in vitro have proved to be too toxic in vivo to be of general use.[7, 8, 9] Consequently, the agents of lesser effectiveness but of greater safety were chosen for investigation by several workers whose published reports, on the whole, have been very gratifying. The results of a comparative study of these same agents, however, have been consistently lacking from the literature. It was indeed fortunate that we were afforded, by a recent pertussis epidemic in this community, the opportunity to make such a study. The purpose of this investigation is twofold; first, to determine the comparative clinical effect of aureomycin, Chloromycetin, and terramycin on 111 cases of uncomplicated pertussis, and second, to determine the effective minimal dose for these drugs. For the sake of completeness and because of the controversy encountered in the literature concerning the clinical effectiveness of streptomycin, it was felt desirable to include a group of twenty-eight streptomycin-treated patients from an earlier epidemic.

From the Department of Pediatrics, Charles V. Chapin Hospital.

I. CASE SELECTION

In order for a patient to be included in the study, certain criteria for diagnosis had to be fulfilled since at times it is very difficult to distinguish between a severe bronchitis and a true pertussis. Two of the following criteria were present in all children included in this study: (a) isolation of *H. pertussis* organism, (b) leucocytosis with absolute lymphocytosis, (c) observation of typical paroxysmal coughs by two or more qualified observers.

A careful history was taken in each instance with particular attention being paid to the exact time of onset of catarrhal symptoms. An attempt was made to elicit a history of recent exposure to the disease within the

family. A careful interrogation of the parent to determine the exact immunological status of the child in regard to pertussis was also made. The latter information was used in the attempt to determine the effect of pertussis immunization on the course of the disease.

II. CLINICAL AND LABORATORY OBSERVATIONS

Each child was observed closely by ward nurses who were instructed in the very important supportive care of pertussis patients. All severely ill patients were assigned special nurses who observed them continuously during the whoop stage. An accurate chart was kept in all instances on which typical whoops, paroxysmal coughs, and vomiting were recorded. These records were checked against notes written by other observers assigned to the cases and were found, in all, to be in close agreement. Fluctuations in temperature and weight were also noted.

Laboratory investigation pertinent to the study included a complete blood count and an attempt to isolate the causative organism. All patients included showed a definite leucocytosis with an absolute lymphocytosis. A cough plate, streak plate, or both, were taken in the majority of patients and were considered positive only after typical colonies were noted and the organism subcultured and agglutinated with type-specific rabbit antisera. Other laboratory tests performed, such as pertussis antibody titers, will be considered in a later study.

III. BASIS FOR COMPARISON

In order to gain a true basis of comparison, observations of in vitro studies by other investigators were utilized. It was noted that effective concentrations in vitro of the three antibiotics (aureomycin, Chloromycetin, and terramycin) used in this study were approximately the same,[1, 2, 3] and assuming other factors to be constant, the three drugs should possess approximately equal therapeutic effect when used clinically. An effort was made, therefore, on the basis of other clinical reports[18, 21, 24] to arrive at a minimal effective dose and to utilize this dose as a standard for all three drugs being investigated. The dose of 50 mg. per kilogram per twenty-four hours was selected for each of the antibiotics used (aureomycin, Chloromycetin, and terramycin). The streptomycin-treated group was not subject to this dose standardization because it was taken from an earlier epidemic and the dose compares to standards of investigation at that time. A group of twenty-one untreated patients was selected from the hospital files to be used as a control group. This was done because a great many of these records were available for study, and it was deemed inadvisable, in the current epidemic, to deprive any child of treatment thought to be of some therapeutic value. These patients represent twenty-one consecutive admissions which fulfilled our diagnostic criteria.

IV. CONSIDERATION OF THE INDIVIDUAL DRUGS IN RELATION TO CONTROL GROUP

Streptomycin (twenty-eight cases).—The use of streptomycin, by the intramuscular and/or aerosol routes of administration, was attended by disappointing results in a group of twenty-eight cases of uncomplicated

pertussis. This group followed the control group closely in age distribution. In spite of the fact that the duration of symptoms at the time of hospital entry was, on the average, somewhat shorter than in the control group, the institution of streptomycin therapy had little or no effect in shortening the cough stage of the illness, the total hospital stay, or the total length of illness. There was a slight reduction in the average length of the whoop stage to 10.6 days (control group, 13.0 days). There was noted in this group a more persistent elevation of temperature, lasting, on the average, more than twice as long as in the control group.

The dosage schedule varied somewhat in this group; the majority of the children received total daily doses of 1 Gm. of streptomycin. In a few instances, daily doses of 1½ and 2 Gm. were administered. The total course of streptomycin averaged approximately 7½ Gm. Further, twenty-two of the twenty-eight patients received one or more injections of pertussis antiserum during the first week of hospitalization.

A review of the literature revealed a wide divergence of opinion concerning the value of streptomycin in the treatment of pertussis. Dowling,[10] Leichenger and Schultz,[11] Gordon and Almaden,[12] Seraphico,[13] and Wannamaker and associates[14] have all reported beneficial effects on the course of pertussis with the use of streptomycin. In contrast, Schwabacher and collaborators[15] and Hoyne and Brown[16] have not been impressed with the efficacy of streptomycin in modifying the clinical pattern of pertussis. Our results tend to agree with the latter two reports.

Aureomycin (twenty-two cases).—Aureomycin was administered at the dosage of 50 mg. per kilogram per twenty-four hours to a group of twenty-two children. The average amount of drug utilized in the course of therapy was 4.6 Gm. Over half of the patients fell in the age range of 0 to 12 months, and the over-all age distribution was similar to that of the control group. The most notable finding with the use of aureomycin was a substantial decrease in the duration of the whoop stage of illness. However, the average duration of the cough stage and the period of hospitalization were unaltered.

In this group of children an attempt was made to give the antibiotic orally in all instances. In a few patients, the aureomycin seemed to incite more frequent vomiting. When this was associated with loss of the drug, the dose was repeated orally after an interval of twenty to thirty minutes. Occasionally, it was necessary to resort to the rectal route for short periods of time. Weight gains in these patients were not impressive, with many of the children showing no weight increments or actual losses in weight. The average figure for weight change was a loss of 1.4 ounces. Temperature elevations were more persistent, averaging 3.8 days as compared to 2.0 days for the control group. The explanation for this finding was not advanced.

The recent literature contains but few references to publications dealing with clinical appraisals of aureomycin in the treatment of whooping cough. Bell and associates[17] have reported favorable results with prompt but gradual diminution in the frequency and intensity of coughing paroxysms. Similarly, Chang and co-workers[18]

have noted aureomycin to be efficacious in favorably modifying the paroxysmal stage of the disease. They have further demonstrated a fairly prompt disappearance of *H. pertussis* from the nasopharynx in their treated cases. Using a comparatively much higher dose of aureomycin, Miller and Ross[19] have obtained gradual and steady improvement in a small series of extremely ill children.

We believe that aureomycin is of definite value in the treatment of pertussis but that our results were not quite as favorable as those reported by others. It is significant, however, that no failures occurred in response to this drug.

Chloromycetin (thirty-six cases).—The use of Chloromycetin was considered successful in thirty-four out of thirty-six cases in this series. The arbitrary standard dose was closely adhered to with the following clinical results. The most important change was the shortening of the whoop stage to 5.5 days as compared to 13 days in the control group. The average shortening by 7½ days of this potentially dangerous stage is considered the most significant clinical response to the drug. The relatively slight shortening of the cough stage is significant only in that it reflects a somewhat earlier recovery from the disease than the control group. The temperature was noted to drop rapidly to normal in response to this drug with a fairly rapid lessening in general toxicity. The drug was well tolerated by mouth in all patients and in no instance was it necessary to resort to the rectal route. There was a small but persistent average weight gain during the hospital stay. This amount was less than that gained by the control group but may be explained by a slightly shorter required period of hospitalization seen in this group. The average total length of the disease showed only slight change from the control group and probably is of no significance. At the standard daily dose, the average total drug required to achieve a satisfactory clinical response was 5.5 Gm.

Payne and collaborators[20] reported dramatic and rapid clinical improvement in a series of pertussis patients treated with this drug during an epidemic in Bolivia. Gray[21] likewise reported very favorable results with the use of Chloromycetin in pertussis, as have Macrae[22] and Degenhardt.[23] While we were unable to duplicate the rapid and dramatic subsidence of symptoms reported by these workers, we believe that Chloromycetin plays a definite role in modifying the clinical course of pertussis, as evidenced by the substantial reduction effected in the duration of the whoop stage.

There were two patients who failed to respond to Chloromycetin. These will be discussed with the failure group.

Terramycin (forty-one cases).—The use of terramycin was considered successful in thirty-eight out of forty-one pertussis patients. The drug was given in the standard dose of 50 mg. per kilogram per twenty-four hours, with the following clinical results as compared to the control group. The most significant clinical change noted was the shortening of the whoop stage by 8.4 days as compared to the control group. The temperature was noted to drop rapidly in response to the drug, and there was a general lessening in the appearance of toxicity fairly soon after the initiation of therapy. The cough stage was shortened only

slightly when compared with the control group and this change was probably of no significance. The drug was tolerated well by most of the children. It was necessary to use the rectal route of administration in only three patients. When the rectal route was used, the dose was increased by 25 per cent. We noted few, if any, definite intolerances to the drug when given orally or rectally at the standard daily dose. A relatively good weight gain was also noted in this group which may reflect the satisfactory tolerance for the drug. The average period of hospitalization was about three days shorter than in the control group, and the total length of the disease showed a ten-day reduction. The latter may be explained on the basis of a relatively shorter length of present illness prior to admission to the hospital in this group. The average total amount of drug required for satisfactory clinical results was 6 Gm.

Jackson and co-workers,[24] Finland and associates,[25] and King and collaborators[26] have reported favorable results in short series of patients treated with this drug. We feel that terramycin has a definite place in the treatment of pertussis; however, we have failed to obtain the rapid or dramatic response to the drug as reported by others.

There were three patients who failed to respond to terramycin and these will be discussed with the failure group.

Combination (five cases).—A short series of five cases was selected to determine the effect of aureomycin, Chloromycetin, and terramycin in combination. The three possible combinations, e.g., aureomycin and Chloromycetin, Chloromycetin and terramycin, and aureomycin and terramycin, were utilized in an effort to discern any appreciable difference in their action. The drugs were given in the standard dose simultaneously; therefore, each patient received twice the total amount of drug daily. Even at this large dose, there was no significant change when compared to the results obtained by singular administration of the drugs. The whoop stage, in fact, was a little longer, as was the cough stage. This suggests that these drugs may not be fully synergetic in action when used together. Definite conclusions cannot be drawn from such a short series of cases; however, we feel our results suggest that no advantage is gained by giving these drugs in combination.

Failure Group (twelve cases).—This group represented the failures to treatment with aureomycin, Chloromycetin, and terramycin when administered singularly or in combination. A failure constituted any patient who failed to respond adequately to 10 Gm. of the test drug or drugs when given at the standard dose of 50 mg. per kilogram per twenty-four hours for each drug. It is noteworthy that there were no failures among the aureomycin-treated group. Two failures occurred in the Chloromycetin-treated group, and three failures occurred among the terramycin-treated group. These were not included in the clinical comparison of the respective groups because all the failures demonstrated a similar pattern of absolute refractiveness to therapy and would thereby be of no significant value when considering the comparative therapeutic action of the drugs. The remaining seven patients in this group were absolute failures to all efforts of treat-

ment. The three test drugs were given in all combinations with absolutely no effect. These cases were also given human and rabbit antisera in adequate recommended doses with no demonstrable result.

1. *Age* (Fig. 1).—Because of the wide age range (3 weeks to 9 years), a method of considering ages by groups had to be devised in order to gain a true prospective of the distribution. This method consisted of dividing the patients into groups corresponding to each six-month period prior to the age of 2 years and each twelve-month period thereafter. The average or mean age for the entire study was just under 1 year of age. It is of importance to note that over one-quarter of the group was under the age of 6 months, and that it was in this group the most severe form of the disease was seen. Over 50 per cent of the children were below the age of 1 year, and 75 per cent were under the age of 3 years. The remainder were scattered fairly evenly in the age range of 4 to 9 years.

YEAR	MONTH	UNT.	STREP.	AUREO.	CHLORO.	TERRA.	COMB.	FAIL.	TOTAL
1	1-6	7	10	6	9	10	2	3	47
	7-12	4	8	7	5	6	1	3	34
2	13-18	1	3	1	3	5	1	1	15
	19-24	1	1	2	1	4	1	1	11
3	25-30	2	1		2	2		1	8
	31-36			1	4	4		1	10
4	37-42		1						1
	43-48		2	1	2	1		1	7
5	49-54				2				2
	55-60	2	1	1	1	2			7
6	61-66								0
	67-72	1		1				1	3
7	73-78								0
	79-84	2	1	2	2	2			9
8	85-90								0
	91-96				1				1
9	97-102								0
	103-108	1			2	2			5
		21	28	22	34	38	5	12	160

Fig. 1.—Average age distribution. *Unt.*, Untreated; *Strep.*, streptomycin-treated group; *Aureo.*, aureomycin-treated group; *Chloro.*, Chloromycetin-treated group; *Terra.*, terramycin-treated group; *Comb.*, combination treated group; *Fail.*, failure to treatment group.

2. *Sex* (Fig. 2).—The sex distribution was about equal. There were 83 females (52 per cent) and 77 males (48 per cent). It has been felt by some writers that pertussis occurs

In this group, which represents about 10 per cent of the patients treated in this epidemic, there was demonstrated a refractiveness to treatment which was not overcome by aureomycin, Chloromycetin, terramycin, or any of their combinations. In spite of reports to the contrary, it appears that the *H. pertussis* organism may be demonstrating an altered sensitivity to these drugs. This phenomenon may account for the reported failures and, more important, may account for the apparent increase in the failure rate noted in the current epidemic subsequent to the preparation of this paper.

V. POINTS OF COMPARISON

Eleven points of comparison were noted in each group and each is discussed briefly below:

more frequently in males than in females. In our experience, we found no significant difference in the incidence of the disease based on sex distribution.

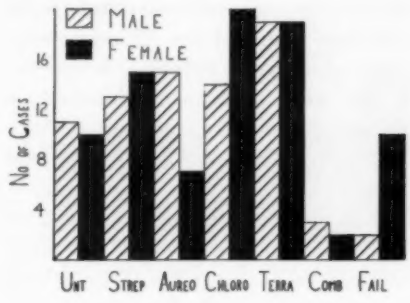

Fig. 2.—Sex distribution.

3. *Present Illness* (Fig. 3).—Special effort was made in taking the history to elicit the exact time of onset of catarrhal symptoms. The period of time between the onset of symptoms and admission to the series was considered the present illness. The average length of symptoms prior to admission for the series was 13.04 days. The deviation from the average may be noted in Fig. 3.

4. *Previous Pertussis Immunization.*—An attempt was made to obtain a detailed history of previous immunization procedures. Those who gave a history of a completed course of pertussis inoculations were included in the immunized group. Those who were not sure of the exact status or were vague in their answers were placed in the unknown group. Those who gave a history of only a partially completed course of pertussis immunization were included in the partially immunized group, and a final group was made up of those who gave no history of immunization. It must be emphasized that it is at times difficult if not impossible to rely entirely on statements which may be colored by ignorance, misinformation, or pride. Our figures for this series were as follows:

Immunized	20.7%
Partial immunization	3.1%
No immunization	57.8%
Unknown	18.4%

We could determine no significant difference in the course of the disease between those who had been immunized and those who had not.

5. *Temperature* (Fig. 4).—The temperature was taken on all patients six times daily until a normal reading was observed for forty-eight hours. Fig. 4 shows the average length of time the temperature remained elevated after the initiation of treatment. The aver-

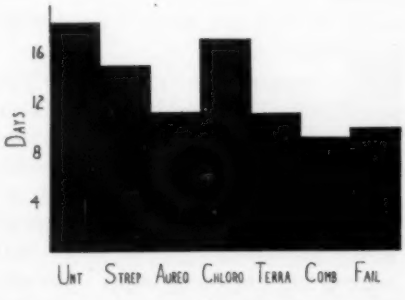

Fig. 3.—Average duration of the present illness (average length of catarrhal symptoms prior to initiation of therapy).

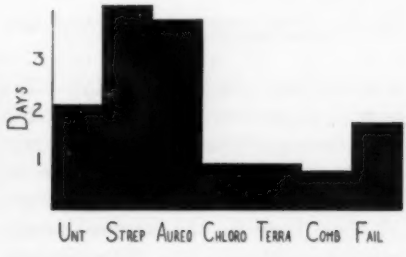

Fig. 4.—Average duration of an elevated temperature after the initiation of therapy.

age length of elevated temperature for the entire series was 2.09 days. It was interesting to note that the temperature remained elevated for a prolonged period of time in the streptomycin- and aureomycin-treated groups. This phenomenon has been noted fairly commonly in patients treated with streptomycin for other conditions. Usually, however, upon discontinuing the streptomycin, the temperature would fall rapidly to normal. The reason for the prolonged temperature elevation in the aureomycin-treated group is not clear but the mechanism involved may be similar in both groups. In the Chloromycetin, terramycin, combination, and even the failure groups, there was a prompt and rapid decline of the temperature to normal.

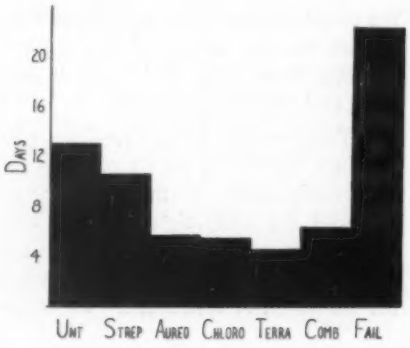

Fig. 5.—Average length of whoop stage after the initiation of therapy.

6. *Whoop Stage* (Fig. 5).—The whoop stage was considered as that time during which was noted the typical paroxysmal type of cough as described by Top.[27] The average length of this stage in the various groups may be noted in Fig. 5. The most significant change, as compared to the control group, was the shortening of this stage in response to terramycin, Chloromycetin, and aureomycin. The speed of response to these drugs was about equal, with the terramycin group showing a somewhat more rapid response than did the Chloromycetin and aureomycin groups. When the drugs were used in combination, a similar but slightly less marked shortening of the whoop stage likewise was noted.

The streptomycin-treated group, on the other hand, showed only a slight decrease in the duration of the whoop stage when compared to the control group. It is of interest to note that the prolongation of the whoop stage in the failure group was far beyond that of the untreated control group. This, we believe, suggests that the severity of the disease among the control group was probably less than that encountered in the current epidemic. Had we felt it justifiable to omit treatment in a group of patients from this epidemic to use as a control group, the results might have been more striking. Since it is currently believed that most of the damage from pertussis occurs during the whoop stage, we believe that any method which will safely shorten this stage of the disease is desirable.

7. *Cough Stage* (Fig. 6).—The cough stage was considered to be that phase of the illness during which there was a persistent but softer and much less severe cough which could be readily distinguished from the typical severe paroxysmal type of cough considered in the whoop stage. As can be noted in Fig. 6, there is no marked shortening of this stage in any of the

groups. The Chloromycetin- and terramycin-treated groups showed only a slight shortening. The cough stage of the failure group was, again, markedly prolonged beyond that of the untreated group.

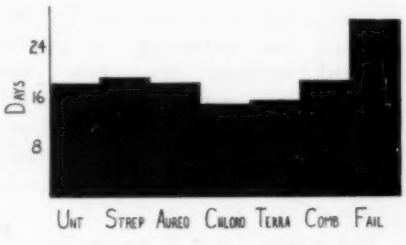

Fig. 6.—Average length of cough stage after the initiation of therapy.

8. *Weight Change* (Fig. 7).—Fluctuations in weight were not marked in any of the groups considered. It may be pointed out that in all but the aureomycin-treated patients there was a small but consistent weight gain. Because of a longer hospital stay, the greatest average weight gain was seen in the failure group. The streptomycin-, terramycin-, and combination-treated groups ranked very closely in their average weight gains. The Chloromycetin group showed the least average weight gain. The aureomycin-treated group showed a very small average weight loss which may be explained on the basis of a slightly greater incidence of vomiting in this group.

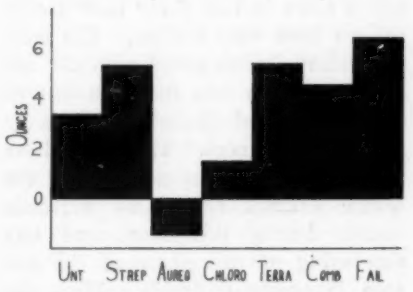

Fig. 7.—Average change in weight during hospital stay.

9. *Hospital Stay* (Fig. 8).—The average length of hospitalization was 20.14 days for the entire group. The Chloromycetin- and terramycin-treated group showed a slight reduction in the required period of hospitalization. The failure group showed a moderate prolongation (25 days).

Fig. 8.—Average length of hospitalization.

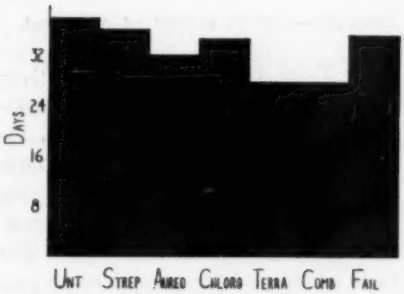

Fig. 9.—Average total length of disease (present illness plus hospitalization).

10. *Total Length of the Disease* (Fig. 9).—This was determined by adding the duration of catarrhal symptoms prior to admission (present illness) and the period of hospitalization. There was noted a shortening of the disease in all groups when compared to the control group. The greatest

reduction occurred in the terramycin- and combination-treated groups. We believe, however, that this reduction was more apparent than real and may be accounted for in the relatively shorter present illness. Since a shortening of this period permits treatment to begin earlier in the course of the disease, a relative reduction in the total length of the disease is to be expected.

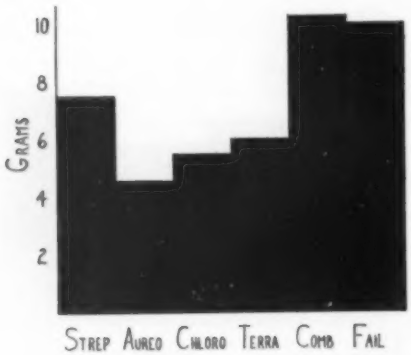

Fig. 10.—Average amount of drug used.

11. *Total Drug Used* (Fig. 10).—Streptomycin was given in all recommended routes of administration, intramuscular, aerosol, and in combination. The daily dose was varied. As can be seen in Fig. 10, the average total dose given was 7.46 Gm. The total amount of drug required to produce a satisfactory clinical response in the aureomycin-, Chloromycetin-, and terramycin-treated groups varied only slightly. In the combination-treated group, the total amount of drug used was by necessity double that of aureomycin, Chloromycetin, or terramycin alone because the standard dose of each drug was given simultaneously.

DISCUSSION

One hundred sixty cases of pertussis were considered in this study. From the current epidemic of roughly 1,200 reported cases of pertussis in this community, 111 hospitalized cases were selected to determine the comparative clinical effect of aureomycin, Chloromycetin, and terramycin on uncomplicated pertussis. To complete the study, a group of streptomycin-treated patients and a group of untreated patients were selected from the hospital records and were analyzed on the basis of the current investigation.

The results noted in the streptomycin-treated group were, on the whole, disappointing. The temperature remained elevated twice as long as did the control group. This phenomenon, however, is rather commonly observed in other patients being treated with this drug. There was only a slight decrease in the whoop stage and the cough stage was not significantly altered. It was interesting to note that no untoward reaction, complications, or sequelae were recorded even though rather substantial doses (averaging 7.46 Gm.) of the drug were administered.

Aureomycin, Chloromycetin, and terramycin will be discussed as a group since in this study their major actions were very similar. The most significant change noted with the use of these drugs was the reduction in the duration of the whoop stage by about 60 per cent. This we believe to be significant because much of the severe damage caused by pertussis occurs during this stage and any shortening of this phase of the disease is surely desirable. With the exception of aureomycin, the average

duration of elevated temperature was markedly shortened. Chloromycetin- and terramycin-treated groups showed a slightly shorter cough stage; however, this is probably not significant. The total amount of drug needed for the treatment of pertussis and that to date they are the safest effective drugs we have to offer; *however*, we believe that the specific drug for the complete and successful treatment of pertussis still lies in the future.

	NO. CASES	AGE	TEMP.	PRESENT ILLNESS	WHOOP	COUGH	TOTAL DRUG	WT.	STAY (DAYS)	TOTAL LENGTH
I. *Untreated*										
Control	21	31.7	2.08	18.3	13	18		+3.4	20	38.1
II. *Treated*										
Aureo.	22	21.6	3.8	11.2	5.7	18.1	4.6	-1.4	21.1	32.3
Chloro.	34	33.1	0.9	17.0	5.5	14.7	5.5	+1.5	17.6	34.9
Terra.	38	26.5	0.9	11.0	4.6	15.4	6.0	+5.4	17.0	28.0
Comb.	5	11.2	0.8	9.2	6.4	18.4	10.24	+4.6	18.8	28.0
Fail.	12	21.4	1.8	9.8	22.4	24.1	10.0	+6.4	25.1	35.5
Strep.	28	17.6	4.4	14.8	10.6	19	7.46	+5.3	21.4	36.3

Fig. 11.—A composite chart of the comparative results of the entire series.

favorable clinical results varied only slightly among the three drugs with the aureomycin group requiring slightly less, the Chloromycetin group second, and the terramycin group the most. There was a small but consistent weight gain in all except the aureomycin-treated group which showed an average weight loss of 1.4 ounces. This loss may be explained on the basis of slightly more frequent vomiting noted in this group. There was no significant change among the three groups in the period of hospitalization. The total length of the disease was shortened in all three groups with the terramycin-treated group showing the greatest change.

It should again be emphasized that the action of these drugs in our hands was not as rapid or dramatic as reported by other investigators. This may be explained on the basis of our slightly smaller daily dose. We feel that aureomycin, Chloromycetin, and terramycin *all* have a definite place in

SUMMARY AND CONCLUSIONS

1. One hundred sixty cases of uncomplicated pertussis were presented.

2. Our results indicated that the use of streptomycin was only of questionable clinical value.

3. Aureomycin, Chloromycetin, and terramycin were considered of almost equal clinical value.

4. We believe the effective minimum dose for aureomycin, Chloromycetin, and terramycin to be 50 mg. per kilogram per twenty-four hours. At this dose, very few intolerances were noted.

5. There is no therapeutic advantage gained in giving the drugs in combination.

6. The relatively higher failure rate seen subsequent to the preparation of this paper suggests that the *H. pertussis* organism may be demonstrating an altered sensitivity to the test drugs.

7. We believe that the specific drug for the complete and successful treatment of pertussis remains still with the future.

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TERRAMYCIN IN TREATMENT OF PNEUMONIAS OF CHILDHOOD

A Report of Ten Cases

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TERRAMYCIN, a new antibiotic, has recently been clinically investigated by several groups and promises to become a valuable aid in treating many of the infectious diseases.[1, 2, 3, 4] Preliminary experimental studies show that the drug is effective in many coccal, bacillary, and some viral infections, yet causes few toxic reactions.[5]

Ten cases* of bacterial pneumonia were treated with terramycin on the Pediatric Service at Freedmen's Hospital. Patients receiving the drug were kept under observation from the beginning of administration to the time of discharge.

CASE REPORTS

Case 1.—J. B., a 4-month-old Negro male, entered the hospital Feb. 3, 1950, with a toxic appearance but a normal temperature. X-ray confirmed a diagnosis of bilateral bronchopneumonia. The blood cultures were all negative, but the nose and throat cultures revealed pneumococci group B and staphylococci. He was given 1.8 Gm. daily (300 mg. every four hours) of terramycin orally. All clinical and roentgenographic signs of illness disappeared by the fifth day of hospitalization.

Case 2.—S. A., an 8-year-old Negro female, entered the hospital Feb. 9, 1950, with physical findings and x-ray confirmation of bronchopneumonia. She had ben ill ten days prior to admission and appeared very toxic. This patient had been admitted to the hospital on previous occasions for treatment of sickle-cell anemia. Prior to admission, penicillin had been administered with no apparent benefit. Blood cultures were negative, but nose and throat cultures revealed hemolytic *Staphylococcus aureus*. She received 1.8 Gm. of terramycin orally for eight days, then 3.0 Gm. (500 mg. every four hours) for four days. The temperature returned to normal in six days, and the x-ray cleared in eight days. No untoward reactions were observed. The patient made an uneventful recovery.

Case 3.—G. H., a 17-month-old Negro male, entered the hospital Feb. 11, 1950, with clinical findings and x-ray confirmation of left lobar pneumonia. He had been ill for six days before admission. A blood culture was negative, but the nose and throat cultures demonstrated staphylococci and streptococci. The patient also had a positive Kahn reaction. He was given terramycin orally in daily doses of 1.8 Gm. for three days, then 3.0 Gm. for three additional days. At the end of four days the temperature was normal, and the x-ray showed complete clearing.

Case 4.—H. M., a 6-year-old Negro male, entered the hospital Feb. 15, 1950, with physical findings of a right lobar pneumonia. X-ray revealed consolidation involving the entire right lung, associated with a pleural effusion. The patient had been ill for five days before treatment. Blood cultures were negative. *Neisseria catarrhalis* and streptococci were cul-

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Terramycin was supplied by Chas. Pfizer & Co. through the Food and Drug Administration of the Federal Security Agency.

*Some of these cases were reported elsewhere.[1]

tured from the nasopharynx. He was given 3 Gm. of terramycin daily for twelve days. The temperature remained elevated for nine days, but there was complete clearing of the x-ray picture within eight days. No untoward reactions were observed and recovery was uneventful.

CASE 5.—M. B., a 3-year-old Negro female, entered the hospital Feb. 22, 1950, with physical findings and x-ray confirmation of lobar pneumonia involving the right lung. She had been ill for four days prior to treatment. On culture, the blood was negative, but the nose and throat revealed staphylococci and streptococci. She received 3 Gm. of terramycin daily for five days. The temperature returned to normal in twenty-four hours, and the x-ray evidence of pneumonia had disappeared by the sixth day. Recovery was prompt and no untoward reactions were observed.

CASE 6.—C. R., a 6-year-old Negro female, entered the hospital Feb. 27, 1950, with physical findings of lobar pneumonia of the right lung, confirmed by x-ray. She had been ill for fourteen days prior to admission. Blood culture showed no growth but nose and throat cultures revealed *N. catarrhalis*, staphylococci, and streptococci. She received 3 Gm. of terramycin daily for five days. The temperature returned to normal in two days, and the pulmonary lesion cleared in five days. No untoward reactions were observed.

CASE 7.—E. T., a 4-year-old Negro female, entered the hospital March 1, 1950, with physical and x-ray findings of bilateral bronchopneumonia. She had been ill only one day before admission. Cultures of the blood, nose, and throat failed to reveal pathogens. She received 3 Gm. of terramycin daily for four days. This patient developed anorexia, refused medication, and vomited the drug when it was forced. Therefore, the terramycin was administered rectally for two days in dosages of 4.5 Gm. daily (750 mg. every four hours). The patient promptly expelled the rectal administration and developed diarrheal stools. Terramycin was discontinued and penicillin was administered intramuscularly with good results.

CASE 8.—J. N., a 4-year-old Negro male, entered the hospital March 8, 1950, with a four-day history of illness associated with high fever. X-ray of the chest confirmed the clinical diagnosis of left lobar pneumonia. A blood culture was positive for pneumococcus group B on admission. He received 3 Gm. of terramycin daily. The temperature was normal within forty-eight hours, and the x-ray cleared within five days. All subsequent blood cultures were sterile. All symptoms of illness disappeared by the fifth day when his discharge was effected.

CASE 9.—J. T., a 9-month-old Negro female, entered the hospital April 20, 1950, with physical findings and x-ray confirmation of right upper lobe pneumonia complicating whooping cough. An admission blood culture was negative. A cough plate yielded *Hemophilus pertussis*. She was given 3 Gm. of terramycin daily which was vomited infrequently. The x-ray became normal within five days. A cough plate taken on the eleventh day of treatment was negative for *H. pertussis*.

CASE 10.—M. W., a 3-year-old Negro female, entered the hospital May 5, 1950, with a history of whooping cough of three weeks' duration. An x-ray of the chest revealed extensive bilateral bronchopneumonia. Blood culture was negative, but a cough plate was positive for *H. pertussis*. She was given 3 Gm. of terramycin daily. Her temperature fell to normal within two days. Considerable improvement was noted in the x-ray films of the chest five days later and complete clearing occurred in fifteen days. The cough did not subside, however, until the seventeenth day. There was no vomiting of medication,

TABLE I. SUMMARY OF PERTINENT CLINICAL AND LABORATORY DATA OF THE TEN PATIENTS TREATED WITH TERRAMYCIN

NO.	PATIENT	AGE	SEX	DIAGNOSIS	DAILY DOSE (GM.)	DURATION OF DOSE (DAYS)	BLOOD CULTURE	NASOPHARYNGEAL CULTURE	TERRAMYCIN SERUM LEVELS IN μG/100 C.C. (HOURS) 1	2	3	5	12	24	NORMAL TEMP. IN DAYS	X-RAY CLEARED IN DAYS
1	J. B.	4 mo.	M	Bronchopneu.	1.8	24	Negative	Pneumococcus B; staphylococci	.25	2.0					0	5
2	S. A.	8 yr.	F	Bronchopneu.	1.8 3.0	8 4	Negative	Hemolytic *Staph. Aureus*	.67	1.25		1.25		.62	6	8
3	G. H.	17 mo.	M	Lobar pneu.	1.8 3.0	3 3	Negative	Staphylococci; streptococci	.31		.67	1.25			4	4
4	H. M.	6 yr.	M	Lobar pneu.	3.0	12	Negative	*N. catarrhalis*, streptococci			1.25	.67		.62	9	8
5	M. B.	3 yr.	F	Lobar pneu.	3.0	5	Negative	Staphylococci; streptococci	1.25						1	6
6	C. R.	6 yr.	F	Lobar pneu.	3.0	5	Negative	*N. catarrhalis;* staph.; strept.	2.5	2.5		1.0			2	5
7	E. T.	4 yr.	F	Bronchopneu.	3.0 4.5	4 2	Negative	Streptococci; staphylococci	Administration of drug followed by vomiting and diarrhea—result unsatisfactory							
8	J. N.	4 yr.	M	Lobar pneu.	3.0	5	Positive (pneumococcus)	Pneumococcus B; staph.; strept.	2.0		67		.62		2	5
9	J. T.	9 mo.	F	Lobar pneu. Pertussis	3.0	10	Negative	Cough Plate—Positive *H. pertussis*	2.5		1.25			.62	0	5
10	M. W.	3 yr.	F	Bronchopneu. Pertussis	3.0	17	Negative	Cough Plate—Positive *H. pertussis*	2.0		.62	.62			2	15

nor were untoward reactions observed.

DISCUSSION

The ten cases of pneumonia in infants and children treated with terramycin hydrochloride have been summarized in Table I. Two cases were associated with pertussis. There were six cases of lobar pneumonia and four of bronchopneumonia. The children had been ill for an average of four days prior to administration of terramycin. Dosages of terramycin ranged from 1.8 to 4.5 Gm. daily. All of the patients received the drug orally suspended in a syrupy vehicle, except in one patient (E. T.). This child refused the drug and vomited it when forced. Rectal administration was attempted but had to be abandoned because of diarrheal stools. This was the only case which exhibited an unfavorable reaction.

Subsequent to completion of this study, terramycin has become available in a buffered elixir* form of the crystalline hydrochloride salt, which is particularly applicable to pediatric practice. The average duration of treatment was six days. Two patients had received previous therapy of penicillin and sulfonamides. A positive blood culture was demonstrated in only one patient. The results of the nasopharyngeal smears and cultures are presented in Table I. It is well known that in children the organisms found in the nose and throat are not necessarily those producing the pneumonic lesions.

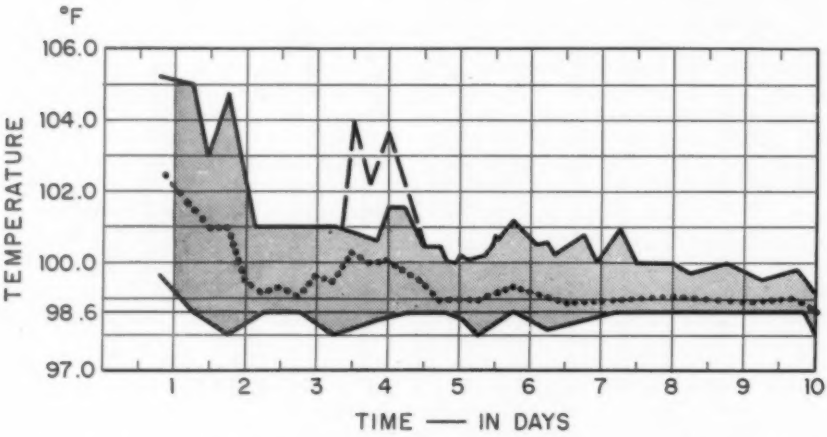

Fig. 1.—Composite graphic representation of the temperature curves in the ten cases starting with the first day of terramycin therapy. The top and bottom solid lines represent the temperature extremes and the middle dotted line indicates the mean. The isolated temperature spike shown by the broken lines depicts the one case (E.T.) which did not respond favorably.

Blood levels were taken on all of the patients and measured in micrograms per 100 c.c. of serum. Of the nine cases which responded favorably to the drug, the temperature curve

*Terrabon, brand of terramycin elixir; combination package consisting of a vial containing 1.5 Gm. of terramycin hydrochloride as the crystalline hydrochloride and a bottle of specially buffered and flavored diluent. When prepared the solution contains 250 mg. of terramycin per teaspoonful. Manufactured by Chas. Pfizer & Co., Brooklyn, N. Y.

fell precipitously to normal (rectally 98.6° to 99.6° F.) in seven cases without return to abnormal levels. In the other two cases there was a partial deflorescence (100° to 101° F. rectally) with persistence at this low-grade level for five and six days, respectively. Graphic representation of the temperature in these cases is seen in Fig. 1.

Our study, as well as that of Melcher and his associates,[4] indicates that terramycin is of value in the treatment of pneumonias in childhood. Another advantage of terramycin is its wide antimicrobial spectrum which includes coccal, bacillary, and viral agents. This is important in pediatric practice where it is often difficult to secure adequate specimens of sputum for specific identification of microorganisms. The fact that the drug is effective when given orally is especially beneficial to the practitioner who must treat many of the patients in the home. Moreover, it is advantageous to have available another effective drug for the treatment of that group of children who have already become sensitized to the sulfonamides and to the other commonly used antibiotics.

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TREATMENT OF TYPHOID FEVER WITH TERRAMYCIN

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IN VITRO studies show that crystalline terramycin hydrochloride[1] is effective against *Salmonella typhosa*. Knight,[2] however, in treating six patients with typhoid fever did not find any evidence of a terramycin-induced response. We are reporting effective results in four of six patients.

All of these patients diagnosed clinically had typhoid fever as judged by fever, diarrhea (often bloody), mental reaction (particularly depression or somnolence, or both), gastrointestinal complaints (distention, tympanitis, and abdominal tenderness), splenomegaly, leucopenia, positive blood and stool cultures for *S. typhosa* (found in one), and the subsequent development of high agglutination titers for *S. typhosa*.

The dosage used was 2 to 3 Gm. daily as a maintenance dose, divided into equal doses given every six hours. In one case, the starting dose was higher than the maintenance. The drug was given orally in capsules, or in the form of an elixir (0.25 Gm. per 4 c.c.). If capsules could not be swallowed, the contents in orange or apple juice were easily ingested. No difficulty in swallowing or retaining the terramycin was encountered and the dosage was continued for six to seven days. If no improvement was noted, chloramphenicol was substituted. This happened to two patients. In the four patients who improved, the terramycin was continued for another seven to eleven days after the fever disappeared.

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Terramycin hydrochloride was supplied gratuitously by the Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

DISCUSSION OF RESULTS

Four patients responded to therapy, two did not. Case 1 (B. J.) received 1.75 Gm. of chloramphenicol before it was discontinued and terramycin therapy substituted. We feel that the chloramphenicol dosage was too small and given over too short a period of time to be curative. It had no effect clinically, or on the temperature which remained between 103° to 105° F. The patient became afebrile forty-eight hours after starting terramycin therapy. Case 2 (A. J.) had no previous therapy, and the longer period for his recovery was possibly due to too small a daily dose (90 mg. per kilogram per day). His recovery was uneventful. Case 3 (M. R.) had no previous therapy and responded well to terramycin. Case 4 (H. R.) received 1 Gm. of chloramphenicol on the seventh day of the disease and this probably was not beneficial. Terramycin produced a clinical response and a return of temperature to normal within ninety-six hours.

In Cases 5 (F. B.) and 6 (W. C.) in which there was no response from terramycin, we feel that the milligram per kilogram dosage was possibly too small.

TABLE I.

CASE NO. CHART NO.	AGE (YR.) SEX RACE	IMMUNIZATION	WIDAL; CULT.; DAY OF DISEASE	DAY OF DISEASE TERRAMYCIN STARTED	TOTAL TERRAMYCIN (GM.)	NO. OF DAYS OF THERAPY	HOURS OF FEVER AFTER START OF THERAPY	REMARKS AND RESULTS
1. B. J. A-8161	2 F N	None	*O 1:320 H 1:640 11th	7th	15.0 200 mg./kg. daily	9	48	Patient was given a total of 1.75 Gm. of chloramphenicol for 2 days before it was discontinued. Terramycin started; rapidly cured patient.
2. A. J. 85326	4 M N	None	O 1:640 H 1:640 15th	15th	24.0 90 mg./kg. daily	12	168	Fever gone in 7 days. Recovered uneventfully. Slow recovery with terramycin. † Dose too small.
3. M. R. 64292	4 F N	None	O 1:640 H 1:320 11th	3rd.	23.0 135 mg./kg. daily	13	96	No previous therapy. Uneventful recovery.
4. H. R. 53181	5 M N	None	O 1:640 H 1:160 9th and 17th	8th	36.0 100 mg./kg. daily	18	96	Given 1 Gm. of chloramphenicol on 7th day of disease. After terramycin therapy started, made uneventful recovery.
5. F. B. A-10816	9 M N	None	O 1:320 H 1:320 9th O 1:640 H 1:160 11th	12th	14.0 80 mg./kg. daily	7	No effect	Fever and clinical condition unchanged on 18th day. Terramycin stopped. Chloramphenicol, 36 Gm., given during next 18 days. Fever disappeared after 96 hr. Uneventful recovery followed.
6. W. C. A-6254	17 M N	None	O 1:640 H 1:320 14th Blood and stool positive 14th	14th	19.5 70 mg./kg. daily	6	No effect	Fever and clinical condition unchanged. 59 Gm. chloramphenicol given during the next 16 days. Fever disappeared after 6 days; uneventful recovery thereafter. Terramycin not helpful; dose may have been too low.

*O = Somatic, H = Flagellar agglutinins.

COMMENT

A one- to three-month follow-up of these patients showed that there were no sequelae, relapses, or carrier states.

We think it important to continue terramycin for seven to ten days after fever disappears to prevent recurrences. If the patient is unable to swallow or retain terramycin, a special form of it can be given intravenously.

No difficulties arose in administering the drug. There were no detectable reactions.

Disease toxicity, gastrointestinal complaints, and leucopenia promptly lessened within two to four days after successful response from terramycin. Fever usually disappeared by lysis within forty-eight to ninety-six hours. This improvement in general well-being was noticeable during this time. Patient H. R. (Case 4) had large depleting bowel hemorrhages, and blood transfusions were given. Within thirty-six hours after starting the drug, the hemorrhages ceased and did not recur, and his infection seemed to be stopped within ninety-six hours.

At present we feel that chloramphenicol[3] is still the antibiotic of choice for the treatment of typhoid fever as there have been too few cases tried with terramycin.

We feel that the dosage of 2 to 3 Gm. daily as recommended is probably too small to cover severe infections. We did not have the facility of sensitivity tests to check this. Since terramycin is a relative nontoxic antibiotic, 100 to 150 mg. per kilogram per day in divided doses should be used in the milder infections and 150 to 200 mg. per kilogram per day in the more severe infections.

SUMMARY

1. Six patients with clinical typhoid fever were treated with terramycin.

2. The terramycin was effective in four cases.

3. In two cases in which terramycin was not effective, the dosage may have been too small.

4. No toxic effects were noted in any of our patients.

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CONGENITAL VALVULAR PULMONARY STENOSIS WITH OR WITHOUT AN INTERATRIAL COMMUNICATION: PHYSIOLOGIC STUDIES AS DIAGNOSTIC AIDS*

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VALVULAR pulmonary stenosis as an isolated lesion and pulmonary stenosis associated with an interatrial communication have been considered to be relatively rare congenital heart anomalies.[1, 2] Accordingly, very little has appeared in the literature describing these two defects. Only one report[2] has appeared in the pediatric literature in which physiological studies have been made on patients with these anomalies.

During the past two and one-half years, we have made physiological studies in over 200 children and young adults with congenital heart disease using the right heart catheterization technique. We have encountered in the course of these investigations nineteen patients with either isolated valvular pulmonary stenosis or pulmonary stenosis accompanied by an interatrial communication. An additional patient was studied who was found to have pulmonary stenosis with a patent ductus arteriosus. The latter was ligated surgically without event. A number of the patients seen by us were thought clinically before these studies were performed to have some other defect.

Since pulmonary stenosis with or without an interatrial communication may be more common than has been previously recognized, and because the method for surgical treatment is quite different,* [3, 4, 5] we are reporting our experience with them.

METHODS

Right Heart Catheterization Technique.—Under sterile precautions, using local procaine anesthesia, a modified No. 8 or No. 9 ureteral catheter was inserted, usually into the left antecubital vein after a cutdown had been made. The catheter was advanced by one member of the team under direct vision, using a fluoroscope operated by a trained radiologist. The free end of the catheter was attached to a three-way stopcock into which could run fluid from a reservoir, or, if the valve was turned, pressure recordings could be made with the connected manometers. Originally, a Hamilton manometer was used, but the majority of these studies were done using a strain-gauge manometer because of its compactness.

The catheter was advanced into the various chambers of the heart where

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*This work was performed under a cooperative agreement between the University of Minnesota and the National Heart Institute, United States Public Health Service, Bethesda, Md.

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*Three of our patients have been successfully operated upon by a direct approach, the details of which are to be reported elsewhere.

pressure recordings were made, and several blood samples were removed under oil for oxygen content analysis. An attempt was made in each patient to get the catheter into both the right and left branches of the pulmonary artery, down the ductus arteriosus (if it was felt that it might be present), into the base and apex of the right ventricle, into two different places in the right atrium, into the inferior vena cava, into anomalous pulmonary veins, through septal defects, and finally in the superior vena cava. Normal values for the pressure and oxygen content of most of these areas have previously been determined. These values plus the direction of change found in a number of the acyanotic conditions can be seen in Table I.

The pressures in the various areas were recorded by means of a camera, using a string galvanometer, which was calibrated against a mercury manometer in millimeters of mercury. The oxygen determinations on the blood were done on a Van Slyke apparatus according to the method of Van Slyke and Neill.

Older children received only atropine premedication. Children under 8 years of age usually required a basal anesthesia. More frequently, rectal Avertin was used; however, occasionally rectal Pentothal was used. The patients received penicillin parenterally before and after the procedure, and penicillin was also placed in the reservoir. A small amount of heparin was likewise added to the solution in the reservoir to prevent any clotting of blood in the catheter. The total fluoroscopic time was regulated by a fluoroscopic timer, and in most instances it was limited to ten minutes.

Oximeter Studies.—Physiological studies on the arterial oxygen saturation were performed in eight of the twenty patients using the modified Millikan oximeter.[6] A base line was established in each with the ear piece in place. Following this, the patient stepped up on a platform one foot high twenty times in rapid succession, and the drop in arterial oxygen saturation was noted. After the oxygen saturation had returned to the base line again, 100 per cent oxygen was administered by mask, and the rise in saturation was noted.

RESULTS

The right heart catheterization results on the twenty patients studied are summarized in Tables II and III. The findings in eight of the patients were interpreted as indicating isolated pulmonary stenosis, in eleven of the patients pulmonary stenosis with an interatrial communication, and in one patient pulmonary stenosis with a patent ductus arteriosus.

Isolated pulmonary stenosis was thought to be present when there was a marked difference in the systolic pressure of the right ventricle (elevated) in contrast to the pulmonary artery (normal or low) and there was no evidence of a left to right or a right to left intracardiac shunt. An interatrial communication (patent foramen ovale or interatrial septal defect) was considered to be present when the catheter was passed through the communication into the left atrium (seven cases) or when there was evidence of a left to right shunt in the right atrium (four cases). One patient, L. J., died during surgical exploration at another hospital. Post-

TABLE I. PRESSURE AND BLOOD OXYGEN VALUES IN VARIOUS CARDIAC CONDITIONS

LESION	INTRACARDIAC PRESSURE IN MM. HG		BLOOD OXYGEN SATURATION IN PER CENT*				
	RT. VENT.	PULM. ART.	VENA CAVA	RT. ATRIUM	RT. VENT.	PULM. ART.	FEM. ART.
Normal	25 ± 5	25 ± 5	75 ± 5	75 ± 15	75 ± 5	75 ± 5	97 ± 3
	0	10 ± 2					
Interatrial defect	Normal or elevated	Same as R.V.	Normal	Increased	Same as R.A.	Same as R.A.	Normal
Interventricle defect	Normal or elevated	Same as R.V.	Normal	Normal	Increased	Same as R.V.	Normal
Patent ductus	Normal or elevated	Same as R.V.	Normal	Normal	Normal	Increased	Normal
Pulmonary stenosis	Elevated	Normal or low	Low or normal	Same as V.C.	Same as V.C.	Same as V.C.	Normal
Pulmonary stenosis with interatrial defect	Elevated	Normal or low	Low or normal	Same as V.C.	Same as V.C.	Same as V.C.	Low
Tetralogy of Fallot	Elevated	Normal or low	Low	Same as V.C.	Increased over R.A.	Same as R.V.	Low
Eisenmenger complex	Elevated	Elevated	Low	Same as V.C.	Increased over R.A.	Same as R.V.	Low
Anomalous pulmonary vein	Normal or elevated	Same as R.V.	Normal	Increased	Same as R.A.	Same as R.A.	Normal

*Oxygen content in volumes per cent divided by oxygen capacity × 100

TABLE II. CATHETERIZATION RESULTS IN PATIENTS WITH ISOLATED PULMONARY STENOSIS

PATIENT	AGE (YR.)	SEX	PRESSURE—MM. HG				OXYGEN CONTENT—VOLUMES PER CENT*					CIRCULATION TIME IN SECONDS		CLINICAL DIAGNOSIS	CATHETERIZATION DIAGNOSIS
			RA	RV	PA	OTHER	VC	RA	RV	PA	FA	ETHER†	FLUOR.‡		
S. K.	9	M	16/4	260/ 0	12/10	-	11.1	10.0	10.4	8.8	18.6 102%	-	-	P.S.	P.S.
J. N.	16	M	-	160/20	12/ 8	-	11.9	11.6	-	11.1	17.7 97%	-	-	IAD	P.S.
R. S.	15	M	6/-4	150/ 0	24/10	-	14.0	12.4	13.5	14.4	20.2	-	-	IAD	P.S.
G. E.	17	F	6/-4	120/ 0	12/ 8	-	13.0	12.7	12.5	12.4	17.2 93%	-	20§	IAD	P.S.
S. H.	6	F	2/-10	90/ 0	28/18	-	10.2	10.4	10.0	11.0	13.3 97%	-	-	PDA	P.S. with PDA
T. R.	7	M	0/-2	80/ 0	7/ 3	-	11.6	13.1	12.4	13.1	17.2 96%	12.0	18.0	P.S.	P.S.
A. H.	15	F	2/-2	40/-8	12/ 2	-	12.0	12.1	12.1	12.2	17.0 99%	-	-	P.S.	P.S.
J. R.	5	M	4/0	50/ 0	20/ 6	-	11.2	11.5	11.9	12.6	16.2 94%	4	9	P.S.	P.S.
C. F.	15	F	-	70/ 0	18/14	-	14.9	15.8	16.0	16.1	18.2 100%	12.0	19.0	Undifferentiated	P.S.

*Oxygen content in volumes per cent determined by Van Slyke analysis.
†Ether circulation time = arm to lung.
‡Fluorescein circulation time = arm to tongue.
§Decohlin circulation time = arm to tongue.
P.S. = Pulmonic stenosis.
IAD = Interatrial septal defect.
PDA = Patent ductus arteriosus.

TABLE III. CATHETERIZATION RESULTS IN PATIENTS WITH PULMONARY STENOSIS WITH INTERATRIAL COMMUNICATION

PATIENT	AGE (YR.)	SEX	PRESSURE—MM. HG				OXYGEN CONTENT—VOLUMES PER CENT						CIRCULATION TIME IN SECONDS		CLINICAL DIAGNOSIS	CATHETERIZATION DIAGNOSIS
			RA	RV	PA	OTHER	VC	RA	RV	PA	FA	OTHER	ETHER	FLUOR.		
D. C.	5	M	0/-8	80/20	12/-6	PV 9/-9	8.7	6.1	4.4	6.4	9.4 60%	PV 14.4	-	5	IVD	P.S. with IAD
L. J.	22	F	10/-4	150/10	10/4	-	8.2	11.0	9.7	8.1	15.6 79%	-	-	-	P.S. with IAD	P.S. with IAD
J. L.	16	F	8/-1	180/0	9/2	LA 5/-2	12.8	12.4	12.1	12.8	16.2 78%	PV 21.5	-	-	P.S. with IAD	P.S. with IAD
J. G.	11	F	2/-2	130/0	2/0	PV 0/-2	15.3	14.5	14.6	13.1	17.4 70%	PV 22.6	4.5	12.0	Eis.	P.S. with IAD
B. B.	8	F	3/2	40/0	3/2	-	13.7	16.4	16.0	13.3	21.1 76%	-	-	-	P.S. with IAD	P.S. with IAD
J. H.	26	M	6/4	95/-10	5/0	PV 5/0	14.0	15.3	15.2	14.1	-	PV 22.1	-	-	P.S.	P.S. with IAD
W. K.	25	M	10/0	154/9	-	LA 8/0	13.7	13.6	-	-	19.3 102%	PV 19.4	8.0	18.0	P.S.	P.S. with IAD
H. L.	16	M	-	30/0	-	LA 4/0	-	15.5	15.2	-	15.2 57%	PV 25.9	8.5	10.0	T.F.	P.S. with IAD
G. A.	9	M	-	120/20	10/0	-	12.1	13.3	14.2	10.2	15.6 78%	PV 20.2	-	4	Eis.	P.S. with IAD
F. S.	21	F	10/0	120/15	12/6	-	11.6	15.8	13.0	12.2	18.8 97%	-	-	-	P.S.	P.S. with IAD
J. S.	8	M	0/-4	60/0	4/2	-	13.2	13.6	15.3	16.0	19.9 87%	-	5	8	P.S with IAD	P.S. with IAD

mortem examination revealed a typical pulmonary valvular stenosis with a poststenotic dilatation of the main pulmonary artery, as seen in Fig. 1, right ventricular hypertrophy, and a large patent foramen ovale.

Fig. 1.—Photograph of heart specimen of patient L. J. who had a valvular pulmonary stenosis with a patent foramen ovale. Arrow points to domelike structure formed by the fusion of the three cusps of the pulmonary valve. Note the size of the opened pulmonary artery.

The range of the systolic right ventricular pressures in the patients was found to be from 40 to 260 mm. Hg, and the range of the systolic pulmonary artery pressures was from 2 to 28 mm. Hg. In general, the higher the right ventricular pressure, the greater were the symptoms and physical findings. As an example, patient S. K., a 9-year-old noncyanotic boy, had a right ventricular pressure of 260 mm. Hg and was unable to walk more than one to two blocks without having to rest. Patient T. R., a 7-year-old noncyanotic male, on the other hand, had a right ventricular systolic pressure of 80 mm. Hg and experienced dyspnea only on extreme exertion.

A valvular type of stenosis was considered to be present when there was a sharp rise in the pressure curve as the tip of the catheter was pulled a short distance from the main pulmo-

nary artery into the right ventricle. This finding was well corroborated by evidence of a poststenotic dilatation of the pulmonary artery.

The right atrial pressures obtained in our study were not strikingly elevated as reported by others.[8] The highest pressure was 16/4 mm. Hg. This occurred in a patient who was not cyanotic. In the five cyanotic patients in whom both right and left atrial pressures were obtained, the pressure gradient was very slight as seen in Table III.

soon as the catheter was withdrawn back through the pulmonary valve into the right ventricle. When the catheter was readvanced a second time through the valve, no changes were noted in the patient's condition.

In the few patients in whom circulation times were performed, the results did not particularly aid in the diagnosis. A few patients had markedly prolonged arm-to-tongue times as has been observed by others.[3]

The results on eight of the patients in whom oximeter studies were per-

TABLE IV. OXIMETER STUDIES

PATIENT	AGE (YR.)	ARTERIAL OXYGEN SATURATION* (%)	SATURATION CHANGE ON OXIMETER FOLLOWING		CATHETERIZATION DIAGNOSIS
			EXERCISE (%)	100% OXYGEN (%)	
J. R.	5	94	-1	+3	Isolated pulmonary stenosis
S. K.	9	97	-3	+2	Isolated pulmonary stenosis
J. N.	16	97	+0.5	+5	Isolated pulmonary stenosis
R. S.	15	97	-1	+10	Isolated pulmonary stenosis
S. H.	6	97	0	+3	Pulmonary stenosis & PDA
G. E.	17	93	-10	+9	Pulmonary stenosis†
J. L.	16	78	-35	+16	Pulmonary stenosis with IAD
D. C.	5	60	-8	+9	Pulmonary stenosis with IAD

*Determined by Van Slyke analysis.

†Oximeter studies and arterial oxygen desaturation indicate patient probably had pulmonary stenosis *with* interatrial communication although heart catheterization did not show it.

Frequently there was a significant drop in the oxygen content of the blood obtained from the pulmonary artery as compared with the right ventricle as seen in Tables II and III. This was attributed to a marked decrease in the cardiac output caused by an additional obstruction by the catheter to the flow of blood through the stenotic pulmonary artery. In the patient S. K., when the catheter was advanced through the pulmonary valve into the pulmonary artery, cyanosis occurred, the heart rate slowed, and the pulse became weak. The patient recovered rapidly within a fraction of a minute from this shocklike state as

formed can be seen in Table IV. From previous studies, we had found in normal children under similar test conditions that the arterial oxygen saturation did not decrease by more than 3 to 5 per cent with exercise. Likewise the oxygen saturation did not increase by more than 3 to 5 per cent when 100 per cent oxygen was administered by mask. In contrast with these results in normal children, we found that patients with a right to left intracardiac shunt (tetralogy of Fallot or nonfunctioning right ventricle) had marked changes in the arterial oxygen saturation with exercise and 100 per cent oxygen. Accord-

TABLE V. CLINICAL FINDINGS IN ISOLATED PULMONARY STENOSIS

PATIENT	AGE (YR.)	SEX	HISTORY			PHYSICAL EXAMINATION					HG. GM. %	PRECATHETERIZATION DIAGNOSIS
			DYSPNEA	CYANOSIS	EXERCISE TOLERANCE	CYANOSIS	CLUBBING	THRILL	MURMUR	P_2		
S. K.	9	M	+++	0	Decreased +++	0	0	S ++ LSB 3	S IV LSB 2 & 3	Abs.	15.7	P.S.
J. N.	16	M	+++	Transient +	Decreased +++	0	0	S + midprecordium	S IV LSB 2	Decr.	15.4	IASD
R. S.	15	M	++	0	Decreased ++	0	0	S ++ Lower LSB	S III LSB 4	Decr.	16.6	IASD
G. E.	17	F	+	0	Decreased +	0	0	S ++ LSB 2 & 3	S III LSB 2	Decr.	14.7	IASD
T. R.	7	M	+	0	Decreased +	0	0	0	S III LSB 2	Abs.	14.2	P.S.
A. H.	15	F	++	0	Decreased +	0	0	0	S III LSB 2	Decr.	13	P.S.
J. R.	5	M	+	0	Decreased +	0	0	S ++ LSB 3	S III LSB 3	Decr.	12.4	P.S.
C. F.	15	F	+	0	Decreased ++	0	0	S ++ LSB	S III LSB 3	Abs.	15.0	Undifferentiated
S. H.	6	F	+	0	Decreased +	0	0	0	Cont. S III LSB 3	Abs.	10.7	PDA

+ = Slight.
++ = Moderate.
+++ = Severe.
LSB = Left sternal border.
S = Systolic.

Roman numerals apply to classification of loudness of murmur.
Arabic numbers indicate interspace of maximum intensity.
P.S. = Pulmonic stenosis.
IASD = Interatrial septal defect.
PDA = Patent ductus arteriosus.

TABLE VI. CLINICAL FINDINGS IN PULMONARY STENOSIS WITH AN INTERATRIAL COMMUNICATION

PATIENT	AGE (YR.)	SEX	HISTORY			PHYSICAL EXAMINATION					HG. GM. %	PRECATHETERIZATION DIAGNOSIS
			DYSPNEA	CYANOSIS	EXERCISE TOLERANCE	CYANOSIS	CLUBBING	THRILL	MURMUR	P_2		
D. C.	5	M	+++ 1 yr.	Transient 1 yr. Persis. 4 yr.	Decreased ++	+	0	S ++ LSB 3	S III LSB 3	Decr.	13.2	IVSD
L. J.	22	F	+ 1 yr.	6 yr.	Decreased +	+	+	0	S III LSB 2	Decr.	14.7	P.S. with PFO
H. L.*	16	M	++ 2 yr.	++ 4 yr.	Decreased ++	+++	++	0	S III LSB 2	Decr.	20.6	T.F.
J. L.	16	F	++	++ birth	Decreased ++	++	++	0	S III LSB 2	N	15.6	P.S. with IASD
J. G.	11	F	+ 2 yr.	++ 4 yr.	Decreased +	++	+	0	S III LSB 3	Decr.	18.5	Eis.
W. K.	25	M	+++	0	Decreased ++	0	0	S ++	S IV LSB 2	Absent	14.9	P.S.
J. H.	26	M	+	0	Decreased +	0	0	S ++ LSB 3	S III LSB 3	Decr.	17.0	IASD
G. A.	9	M	+++	+++ birth	Decreased +++	++	+	S ++ LSB 3, 4	S IV LSB 3	Absent	15.1	Eis.
J. S.	8	M	+++	+ 7 yr.	Decreased +++	+	0	S ++ LSB 3	S IV LSB 2	Decr.	15.0	P.S. with PFO
F. S.	21	F	+	0	Decreased +	0	0	0	S III LSB 2	Decr.	14.5	P.S.
B. B.	8	F	+++	++ birth	Decreased +++	++	+	S + LSB 3	S III LSB 3, 4	Decr.	21.4	P.S. with IASD

*Right-sided aortic arch.

ingly, from Table IV the results on the first five patients, J. R., S. K., J. N., R. S., and S. H. are thought to be compatible with the diagnosis of isolated pulmonary stenosis without any significant right to left intracardiac shunt. The last two patients in Table IV, J. L. and D. C., showed evidence of a right to left intracardiac shunt. This was confirmed during the heart catheterization when the catheter in both instances passed through an interatrial septal defect. From the heart catheterization data in patient G. E., we were unable to demonstrate any right to left intracardiac shunt. The oximeter studies, however, suggest that a small shunt was present.

CLINICAL FINDINGS

The symptoms and clinical findings in patients with uncomplicated valvular pulmonary stenosis has been well reviewed by Greene and associates.[7] These are: varying degrees of cardiac disability from none to severe dyspnea with or without mild cyanosis; a loud systolic murmur over the left precordium with a decreased pulmonary second sound, right axis deviation on the electrocardiogram; right ventricular enlargement with a prominent pulmonary artery segment, decreased root shadows and decreased vascular markings in the lung fields on roentgen examination. In those patients with an interatrial communication, cyanosis is a more prominent feature, the onset usually occurring much later than in patients with a tetralogy of Fallot.

Analysis of the clinical findings in our patients is shown in Tables V and VI. In most instances it agrees with that of Greene.

DISCUSSION

Valvular pulmonary stenosis with or without an interatrial communication is a definite syndrome requiring differentiation from other types of noncyanotic and cyanotic or potentially cyanotic congenital heart disease. The conditions most frequently confused with isolated valvular stenosis in our series of patients were interatrial and interventricular septal defects. The conditions most frequently confused with pulmonary stenosis plus an interatrial communication were tetralogy of Fallot and Eisenmenger complex.

Pulmonary stenosis should be suspected in those patients who have severe dyspnea, in whom the pulmonary second sound is absent or decreased in intensity and roentgen examination reveals an enlarged pulmonary artery that is out of proportion to the vascular markings in the lung fields.

Standard and unipolar leads of the electrocardiogram were of limited value as an aid in the diagnosis. Right heart strain and hypertrophy occurred in patients with septal defects as well. Usually, however, *severe* right heart strain was seen more commonly in those patients who had pulmonary stenosis with or without an interatrial communication.

From our data, the relationship between the atrial pressures and the presence or absence of cyanosis is not clear. Certainly some of the patients had normal right atrial pressures and yet were cyanotic suggesting the existence of a right to left shunt.

Until our experience with this syndrome is more extensive, the correct diagnosis is likely to be made only by

additional special studies such as heart catheterization and oximetry. Oximeter studies should be able to help differentiate the noncyanotic patient with pulmonary stenosis plus an interatrial communication from the patient with isolated pulmonary stenosis.

SUMMARY

Physiological studies using the right heart catheterization technique on twenty patients with pulmonary stenosis with or without an interatrial communication have been presented. The catheterization findings in eight of the patients were interpreted as indicating isolated pulmonary stenosis, in eleven pulmonary stenosis plus an interatrial communication, and in one pulmonary stenosis with a patent ductus arteriosus. Eight of the twenty patients were also studied using the modified Millikan ear oximeter. None of the patients with isolated pulmonary stenosis had cyanosis.

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AN UNUSUAL ANOMALY OF THE AORTIC ARCH

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IN THIS paper, three cases of a cardiovascular anomaly are presented which demonstrate the emergence of the right aortic arches to a position of dominance in the chest. As Congdon[1] has shown, the innominate and right subclavian vessels arise from the same anlage of primitive arches on the right side, corresponding to the origin of the aorta from the left arches, but are relegated to a comparatively minor role by genetic influences later in development.

The six human aortic arches are formed throughout the fourth week and they become transformed into the permanent major vessels during the fifth to seventh weeks. A complete description of these changes can be found in a standard text on embryology.[2] It suffices to point out that the permanent aortic arch is derived from the primitive left fourth arch, the left half of the aortic sac, and a portion of the left dorsal aorta; the right fourth arch together with practically all of the right dorsal aorta forms the right subclavian artery. The right half of the primitive aortic sac elongates into the innominate artery. The left subclavian artery is derived, as a separate outgrowth, from the left permanent aortic arch. The sixth pulmonary arches develop from outgrowths of the dorsal aortas which anastomose with the early pulmonary arteries. The right pulmonary vessel usually loses its connection with the right dorsal aorta, but on the left side this relationship is maintained as an important functioning vessel, the ductus arteriosus, until birth.

Final adjustments usually establish all other derivatives of the primitive arches as what appear to be simple outgrowths of the permanent aorta. In our cases this subordination has been thwarted; the right arches appear to be the progenitors of the major thoracic vessels (Fig. 1*B*).

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CASE REPORT

CASE 1.—Case 12910 was a 5 pound, 2 ounce Negro male infant who was born moderately narcotized, but responded well to resuscitation. Physical examination revealed no abnormalities. The heart size was normal to percussion and no murmurs were heard. Sixteen hours later the infant suddenly became cyanotic and expired. Gestation had been without incident; previous children were normal.

Post-mortem examination revealed a well-developed male infant weighing 2,240 grams. Positive findings included mild cerebral edema and generalized visceral congestion; the heart and the great vessels were grossly malformed.

The heart weighed 17 grams; the myocardium was firm and red-brown. External evidence of interventricular coronary vessels was absent. No septum was present between either the atria or the ventricles; the wall of the ventricle was 4 mm. thick. A single large vessel, 5 mm. in diameter, arose from the base of the ventricle just to the right of midline; it was guarded by a tricuspid semilunar valve. A left and right pulmonary artery were given off from the lateral aspects of this vessel 16 mm. from the base. After ascending 30 mm., the vessel divided into

the two main branches. The left division arched downward to become the thoracic aorta in normal position. It was 8 mm. wide, and it gave off no major vessels in the chest. The right division, 6 mm. in diameter, gently curved laterally and gave rise to the left subclavian and common carotid arteries, and terminated in the innominate trunk which divided normally.

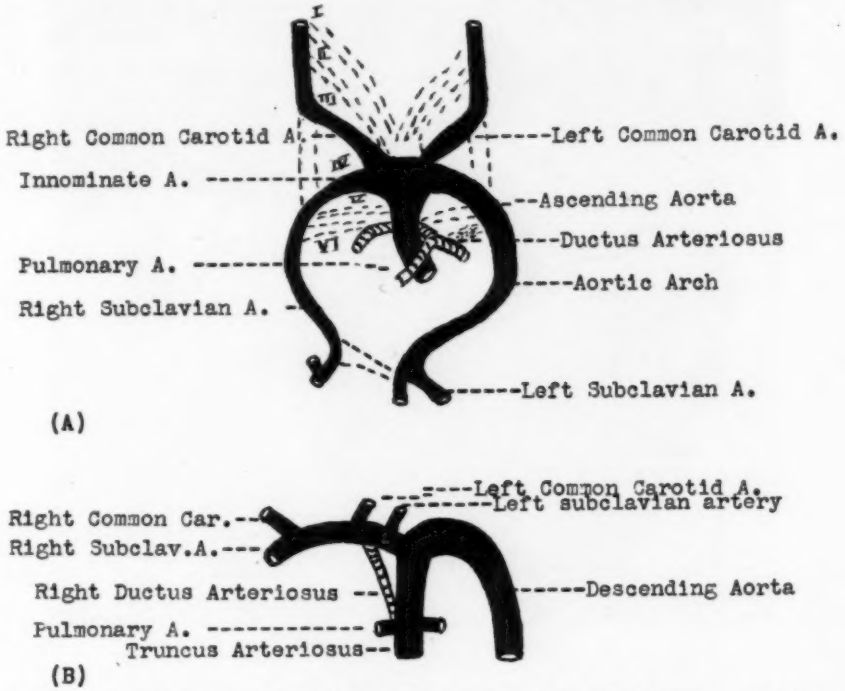

Fig. 1.—*A*, Transformation of the aortic arches (normal). (From Arey's Developmental Anatomy, W. B. Saunders Co.) *B*, Anomaly.

A fibrous cord, 13 mm. in length, arose from the right lateral aspect of the main vessel 10 mm. from its base and joined the right branch vessel opposite the point of origin of the right common carotid artery.

The anatomical diagnosis was:

1. Prematurity.
2. Congenital heart disease.
   a. Cor biloculare.
   b. Truncus arteriosus.
   c. Anomaly of the great vessels.
   d. Right ductus arteriosus.
3. Cerebral edema.
4. Pulmonary atelectasis.
5. Generalized visceral congestion.

Case 2.—Case 11545 was a 5 pound, 14½ ounce Negro female infant, born spontaneously, presenting no physical abnormalities. The infant had good color and a lusty cry; no cardiac murmurs were heard. Eight hours later the patient suddenly became cyanotic and dyspneic and expired within sixty minutes. Prenatal history was negative for infections, trauma, or bleeding; previous children were normal.

Post-mortem examination revealed a well-developed full-term female Negro infant weighing 2,640 grams. Positive findings included cerebral edema, pulmonary edema and atelectasis, bilateral hydrothorax, ascites, and visceral con-

gestion. The heart and great vessels appeared abnormal.

The heart did not appear grossly enlarged, and weighed 19 grams. External evidence of the interventricular coronary vessels was absent. No septae were found between atria or ventricles; the ventricular wall was 8 mm. thick near the base. Arising from the base and common carotid arteries, and an innominate trunk which divided normally; this vessel was 4 mm. in diameter. A distinct fibrous cord extended from the right side of the main vessel, 15 mm. from its base, and joined the innominate vessel just proximal to the origin of the origin of the left subclavian; it was 9 mm. in length.

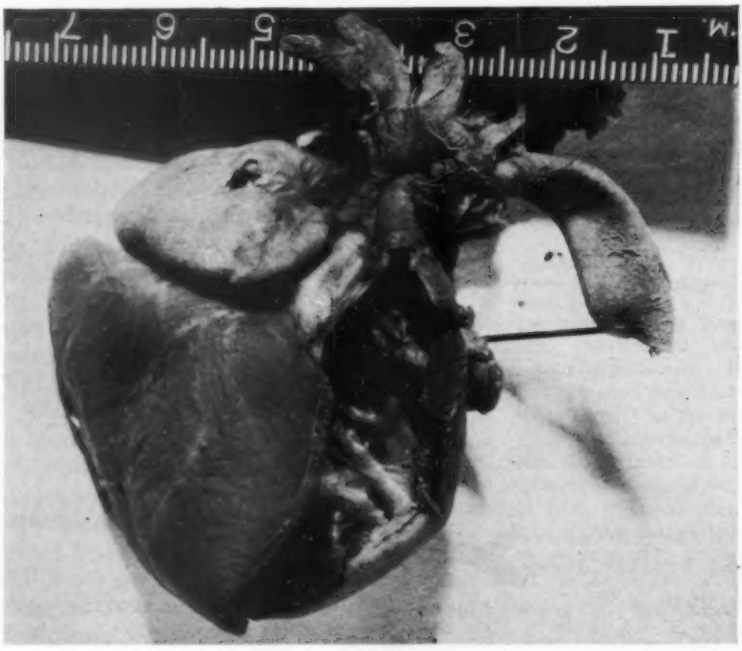

Fig. 2.

of the ventricle was a single large vessel, 5 mm. in diameter, and guarded by a tricuspid semilunar valve. A right and left pulmonary artery were given off to their respective lungs from the lateral aspect of the vessel 10 mm. from the base. The main vessel ascended 10 mm. further and then divided into two main branches. One branch turned left and downward to become the thoracic aorta in normal position; it was 6 mm. in diameter, and gave off no major vessels in the chest. The other branch curved gently to the right, giving origin to a left subclavian

The anatomical diagnosis was:

1. Congenital heart disease.
   a. Cor biloculare.
   b. Truncus arteriosus.
   c. Anomaly of the great vessels.
   d. Right ductus arteriosus.
2. Anasarca.
3. Pulmonary edema and atelectasis.
4. Generalized visceral congestion.

CASE 3.—Case 6624 was a spontaneously delivered 6 pound, 9 ounce Negro male infant who presented no physical abnormalities. He had a good color

and a lusty cry; no cardiac enlargement or murmurs were noted. Twenty-four hours after birth the infant suddenly went into shock and became cyanotic. Respirations were 30 per minute and grunting; heart rate was 40 per minute. The liver edge was palpable 5 cm. below the costal margin. The infant expired two hours later.

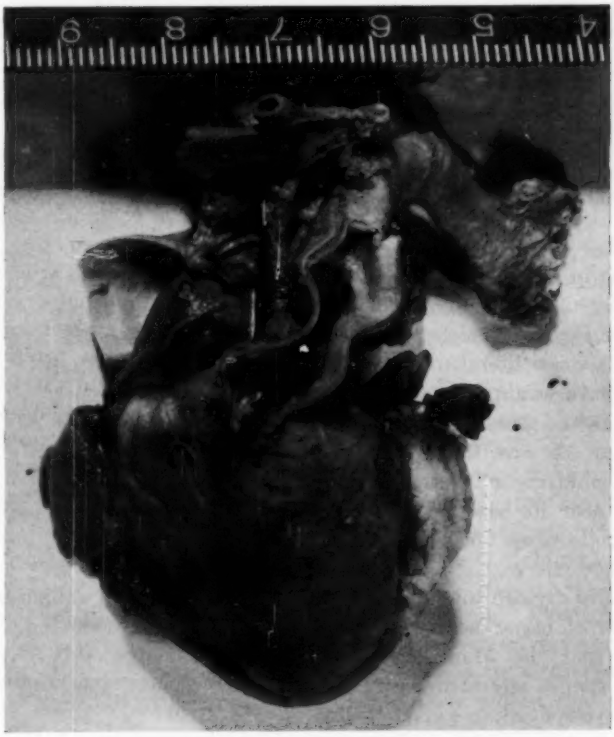

Fig. 3.

Post-mortem examination revealed a well-developed full-term Negro male infant weighing 2,900 grams. Positive findings included pulmonary atelectasis and edema, mild bilateral ascites, and generalized visceral congestion. The heart and great vessels appeared grossly abnormal.

The heart appeared enlarged and weighed 26 grams. No interventricular coronary vessels were noted externally. A single ventricle and a single atrium were present; no evidence of septum formation could be found. The ventricular wall was 3 mm. thick. A single large vessel arose from the base of the ventricle, to the left of the midline; it was 8 mm. in diameter, and was guarded by a bicuspid semilunar valve. A right and left pulmonary artery were given off from the lateral aspects of this vessel 10 mm. from the base. After ascending 18 mm., the main vessel divided into two branches. The left branch turned downward to become the thoracic aorta in normal position; it was 8 mm. wide, and originated no major vessels in the chest. The right branch, 5 mm. wide, curved gently to the right, giving off at its junction with the aorta the left sub-

clavian artery, and then the left common carotid, and the right innominate vessel which divided normally into right common carotid and right subclavian vessels. A fibrous cord, arising from the right anterolateral surface of the main vessel 10 mm. from its base, joined the innominate vessel.

The anatomical diagnosis was:

1. Congenital heart disease.
   a. Cor biloculare.
   b. Truncus arteriosus.
   c. Anomaly of the great vessels.
   d. Right ductus arteriosus.
2. Pulmonary atelectasis and edema.
3. Hydrothorax, bilateral.
4. Ascities.
5. Generalized visceral congestion.

DISCUSSION

Variation in the number of branches given off by the aortic arches is considerable. Poynton[3] collected cases from the German literature in which the aorta gave origin to a single vessel. They were described as of two major types. In one, the aorta is described as splitting off from its lone derivative near its base, while in the other, a single vessel springs from the top of the aortic arch. The solitary vessel usually divided into the normal complement of major vessels. It was suggested that the branches of the aorta had simply migrated, through a freak of development, to a single point. In our cases, although the main vessel divides from a truncus arteriosus, it is comparable to the first type described by Poynton. Fig. 2 (Case 2) demonstrates the truncus arteriosus arising from a single ventricular chamber with a single large vessel branching off from the arch of the aorta and giving rise to the innominate, the left common carotid, and the left subclavian arteries. The short fibrotic ductus arteriosus is also visible. The presence of this large right-sided curving vessel terminating in the innominate and right subclavian arteries may be explained by absence of subordination of the right fourth aortic arch; however, the origin of the left common carotid and subclavian vessels from this arch can not be explained in this manner.

A right-sided ductus arteriosus is described as a rare anomaly.[3] It usually joins either the proximal portion of the right subclavian, or the innominate artery just before its division. Taussig[4] states that a ductus may or may not be present in conjunction with a truncus arteriosus. When present, it is a fibrotic cord at birth, since the truncus, serving as a common channel for both arterial and pulmonary blood, obviates its function. Fig. 3 (Case 3) demonstrates clearly the fibrotic ductus arteriosus which arises just distal to the valve of the truncus, and extends upward to join the right subclavian artery. Presence of the right ductus seems to be further evidence of lack of subordination of the right aortic arches.

SUMMARY

Three cases of a unique cardiovascular anomaly are described. An explanation is attempted through a review of the embryological development of the aortic arches.

I am indebted to Martin D. Rich for the photographs of the pathology specimens, and to Helen Goldwyn for the line drawings.

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THE ROLE OF THE Rh FACTOR IN THE ETIOLOGY OF CEREBRAL PALSY

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IT HAS been known for almost a decade that maternal isoimmunization to the Rh factor may cause cerebral damage—the syndrome of kernicterus. The clinical manifestations[1] may be choreoathetosis, spasticity, mental defect, plastic opisthotonos, paralysis, ataxia—in short, the classical picture of cerebral palsy. We have attempted to determine how great a role maternal isoimmunization to Rh plays in the causation of cerebral palsy.

In 1937, three years before the discovery of the Rh factor, Klingman and Carlson[2] reported 675 cases of neuromuscular dysfunction characterized by spastic paralysis, choreoathetosis, ataxia, and mental defect. Forty-five (6.6 per cent) of these children had survived a severe neonatal jaundice and subsequently developed neuromuscular dysfunction, mental deficiency, or both. Thirty-eight of the patients had been jaundiced at birth, and three additional ones on the first day. In seventeen, icterus had lasted two weeks or longer, averaging ten weeks. No mention of anemia in the neonatal period was made.

Yannet and Lieberman[3] studied 119 patients with undifferentiated mental defect at the Southbury Training School. The average age was 24 years. All had intelligence quotients under 30. These investigators found nineteen instances in which there was an Rh_0-rh incompatibility between patient and mother. On the basis of statistical and theoretical considerations, they believed that only nine instances of Rh incompatibility would have been discovered in an equal number of normal individuals. They, therefore, felt it reasonable to expect that ten of the nineteen cases of Rh incompatibility may have been examples of cerebral damage due to maternal Rh isoimmunization. Actually, in only six patients was there a history of erythroblastosis fetalis, and in three of these the diagnosis was presumptive.

McGovern and Yannet[4] reported sixty-seven cases of asymmetric spastic cerebral palsy with severe mental defect. They stated that seven (10 per cent) were caused by maternal isoimmunization to the Rh factor. However, six of these seven cases had already been presented in the previous article, and in only three of the six was the history of erythroblastosis fetalis definite.

In 1949, Yannet[5] analyzed 157 cases of infantile cerebral palsy with severe mental deficiency. The average age was 18 years; the average intelligence quotient 25. In this group

From the Dr. Abraham Jacobi Division for Children, Dr. Hugh Chaplin, Director, and the Cerebral Palsy Pre-school Center, Dr. George G. Deaver, Director, the Lenox Hill Hospital.

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he found eight instances in which the cerebral abnormality was attributable to maternal Rh isoimmunization. Again, six of the eight were the ones originally reported.

Evans[6] recently reported 114 cases of cerebral palsy. This was a young group, the average age being 6.4 years. In eight instances (7 per cent) the cerebral damage was due to kernicterus caused by maternal Rh isoimmunization. The diagnosis of erythroblastosis fetalis was made in the neonatal period and confirmed retrospectively. In all eight cases there was child-mother Rh_0 incompatibility. In two instances the maternal indirect Coombs test was positive.

Josephy[7] stated that recent investigations suggested that the role of the Rh factor in the etiology of feeblemindedness was an important one. He felt that this might be true also for infantile cerebral palsy. Keats[8] remarked that erythroblastosis fetalis will frequently result in damage to the basal ganglia with the development of athetosis. On the other hand, Bakwin and Wiener[9] investigated twenty-three young patients with athetosis beginning early in life. Only five of the twenty-three mothers were Rh negative, and in none of these was Rh antibodies discovered. In only three instances was Rh_0 incompatibility present between child and mother. Histories of the neonatal period were not presented in the article.

The following work is an attempt to determine in an unselected group of patients with cerebral palsy the number of cases which had been caused by the cerebral sequelae of erythroblastosis fetalis.

RESULTS

The study was based upon ninety-eight children with cerebral palsy from the Cerebral Palsy Pre-school Center of the Lenox Hill Hospital. All were white. A history was taken from the mother in every case. In the neonatal history attention was focused upon the time when jaundice appeared, its duration, the occurrence of anemia, cyanosis, convulsions, and the administration of transfusions. The developmental progress of the patients was recorded. The mothers were questioned about the ease or difficulty of labor, miscarriages, abortions, and transfusions or the intramuscular injection of blood. The number and age of siblings were noted, as well as their health status and the incidence of possible erythroblastosis fetalis among them.

All the patients received a physical examination. Each child and mother, with one exception, was typed for the Rh factors and the ABO blood groups. In every instance where the mother was Rh negative her serum was tested for anti-Rh antibodies in saline and albumin systems by the standard methods. The typings and antibody determinations were performed under the supervision of Jacob Geiger, M.D.

The age span of the patients was from 8½ months to 12 years. Fifty-eight were 4 years or under; 30 were from 5 to 8 years; and 8 were from 9 to 12 years of age. In two instances the age was not recorded. The age of the mothers was from 22 to 47 years. Forty-four of the mothers were 35 years or older.

The Rh typings are shown in Table I. In ten instances there was an

Rh_0-rh incompatibility between patient and mother.

In twenty-two instances there was an incompatibility between the patient's AB blood groups and the mother's serum.

Eighty-nine patients were tested by the Psychology Department of the Cerebral Palsy Pre-school Center. This was done under the supervision of Bessie B. Burgemeister, Ph.D., and Lucille H. Blum, Ph.D. The intelligence quotients are shown in Table II. Fifty-three per cent of the patients had intelligence quotients of 70 and below—the mental defective group.

ward opisthotonos, and mental defect. L. W., aged 3½ years, was, unfortunately, the only patient in this series who with his mother was not typed for the Rh factors and the ABO blood groups. Labor had been uneventful. The child had been severely jaundiced and anemic at birth. At 3 weeks of age he was taken to another hospital where he received three blood transfusions. There was one healthy, older sibling. The patient sat up at 3 years of age, and does not yet walk or talk. Physical examination revealed spasticity, choreoathetosis, a tendency to opisthotonos, and mental defect. A. W., aged 2 years, was Rh_1. Labor had been induced

TABLE I. Rh TYPINGS ON PATIENTS AND MOTHERS

	Rh_0	Rh_1	Rh_2	Rh_1Rh_2	Rh′	Rh NEGATIVE	TOTAL
Patients	3	47	11	21	1	14	97
Mothers	4	52	10	14	1	16	97

TABLE II. INTELLIGENCE QUOTIENTS ON EIGHTY-NINE PATIENTS

Very superior 130 and above	Superior 120-129	High average 110-119	Average 90-109	Low average 80-89	Boderline	Defective 70 & below
4	1	5	21	8	3	47

Three of the ninety-eight patients had had erythroblastosis fetalis. S. R., aged 4 years, was Rh_1Rh_2. She had been severely jaundiced at birth, and had been transfused three times, on the third, fourth, and fifth days of life. Delivery had been normal. The mother was Rh negative, and her serum contained no anti-Rh antibodies. Both patient and mother belonged to blood group O. There was one older healthy sibling. The patient did not yet sit up, stand, or talk. Physical examination revealed spasticity, choreoathetosis, a tendency to-

prematurely because of possible Rh incompatibility. Delivery was uneventful. Jaundice had become severe on the second day of life, and had lasted for three weeks. No transfusions had been given. The mother was Rh negative, and her serum contained anti-Rh antibodies in an albumin system in a titer of 1:4. Both patient and mother belonged to blood group A. There was one healthy, older sibling. The patient sat up at 14 months, and walked at 2 years of age. Physical examination revealed choreoathetosis and mild spasticity.

Only one other mother had anti-Rh antibodies in her serum. This Rh-negative woman had albumin antibodies in a titer of 1:16. Her first child, L.L., aged 6½ years, one of the cerebral palsy patients in this series, had been delivered by high forceps. He was Rh_1. He had not had erythroblastosis fetalis. There was no history of abortions, miscarriages, or maternal transfusions. Subsequent to the birth of L. L., the mother had a second child who was erythroblastotic and who received a transfusion shortly after birth. The presence of albumin anti-Rh antibodies in the mother's serum merely confirmed the diagnosis of erythroblastosis fetalis in the second child, who is now normal.

DISCUSSION

In this series of ninety-eight white children with cerebral palsy, ninety-seven of the patients and mothers were typed for the Rh factors and the ABO blood groups. Sixteen of ninety-seven mothers were Rh negative. This figure is only slightly greater than the approximately 15 per cent incidence of Rh-negative women in the general white population. Ten of the sixteen children of these mothers were Rh_0 positive. This 63 per cent incidence of Rh-positive children in the Rh-negative mothers' group is roughly the same as in the general population. In the single instance in which the child and mother were not typed for the Rh factor, the patient had suffered from erythroblastosis fetalis. This would not have altered the significance of the figures previously mentioned. In twenty-two of ninety-seven instances there was incompatibility between the patient's AB blood groups and the mother's serum. This is even less than the approximately 25 per cent incidence of such ABO incompatibility found in normal families.[9] From these figures alone it is apparent that a high incidence of maternal isoimmunization to the Rh factor or the AB blood groups would be most unlikely in our series.

Actually, only three of the ninety-eight children had suffered from erythroblastosis fetalis. In only 3 per cent, therefore, of a group of unselected patients attending a cerebral palsy clinic was the condition definitely attributable to kernicterus. Although the incidence of erythroblastotic children in this series was perhaps eight times as high as in the general population, nevertheless it is obvious that maternal isoimmunization to the Rh factor played only a minor role in the causation of cerebral palsy.

Ours was a young group of children, a fact which makes the detection of erythroblastosis fetalis in the neonatal period easier. In spite of this, the percentage of erythroblastotic patients was lower than has been reported in the literature.[2, 3, 4, 5, 6] In Yannet's[5] latest and largest series, eight of 157 patients with cerebral palsy had had erythroblastosis fetalis. In three of these, however, the diagnosis was presumptive. If these are excluded, his percentage coincides with our own.

SUMMARY

Ninety-eight children with cerebral palsy were studied. In only three was the cerebral damage caused by kernicterus.

CONCLUSION

Maternal isoimmunization to the Rh factor plays only a slight role in the etiology of cerebral palsy.

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THE SIGNIFICANCE OF DELAYED DEVELOPMENT IN THE DIAGNOSIS OF CEREBRAL PALSY

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INTRODUCTION

THE rate of development is a reliable measure for predicting normal or abnormal neurologic status during infancy and early childhood.[1] In early life slow development may be the only indicator of cerebral palsy.[2]

Although the range in normal rate of progress is wide, extreme deviations have more serious implications than are often recognized. This is particularly true when more than one developmental item is slow in onset. For instance, although a child may not speak sentences at the usual time and still be normal, if other items such as sitting and walking are also delayed, then failure to speak may indicate a more serious prognosis.

The purpose of this paper is (1) to evaluate the rate of development in cerebral palsied children in order to indicate the diagnostic implications of delayed development, and (2) to present a simple scale based on the rate of development of normal children, by which the practitioner can more easily appraise the brain-injured infant or young child.

MATERIAL AND METHODS

The records of 100 cases of cerebral palsied children were analyzed. Sixty cases are from the Emma Pendleton Bradley Home, Riverside, R. I., which formerly treated cerebral palsied children on an in-patient basis, and forty cases are from the Meeting Street School, Providence, R. I., a cerebral palsy day school predominantly for children of nursery school age. Ages of the subjects at the time of history taking ranged from 6 months to 13 years.

The developmental items selected for analysis were: erection of head from prone, reaching for objects, crawling, sitting without support, prehensile grasp, single words, standing alone, walking alone, and two- or three-word sentences. These items were selected because the information obtained was considered reliable, in that parent histories, wherever possible, were verified by hospital abstracts and the reports of referring physicians.

The standards used for normal and late normal development were those of Gesell and Amatruda.[3]

RESULTS

Developmental Items.—

Head Erection From Prone: The normal infant usually can lift his head upward from the prone position for short periods during the first month of life. It is significant if a baby fails

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to erect head from the prone after 3 months of age. Of seventy-four cerebral palsied children studied 14 per cent could hold their heads erect momentarily by 1 month (normal), 18 per cent by 3 months of age (late normal), while the majority (68 per cent) failed to hold their heads erect from the prone within the expected range. The average age of attaining this item was 12.4 months.

Reaching: The normal infant usually reaches for near-by objects from 3 to 5 months of age. In this study, of twenty-eight cerebral palsied children, 3 per cent reached for objects before 5 months (normal), while 86 per cent reached for objects later than this. Eleven per cent of the cases were reported never to have reached for objects.

Sitting Without Support: The normal infant can usually sit without support from 6 to 8 months of age. It is abnormal if an infant cannot sit independently by 10 months of age. Of seventy-three cerebral palsied children studied, 15 per cent could sit without support by 8 months (normal), 14 per cent by 10 months (late normal), while 71 per cent did not acquire the ability to sit independently until after 10 months. The average age of acquiring this skill was 20.4 months.

Crawling: The normal infant can usually crawl, dragging the body along the floor and drawing his legs after, by 7 months of age, and it is abnormal if this item is delayed beyond 8 months. Of fifty-four cerebral palsied children, only 2 per cent acquired this skill by 8 months. Thirty-seven per cent crawled after this age, and 61 per cent never crawled. The average age of crawling in those who acquired this skill was 26.4 months.

Prehension: The normal infant usually can promptly grasp an object between thumb and forefinger by 9 months, and delay beyond 11 months is abnormal. In this study, of sixteen cerebral palsied children studied, 9 achieved prehension by 9 months (normal) while the remaining 7 were delayed in achieving prehension until after 11 months.

Speech (Single Words): The normal infant can volcalize single words such as "mama," "dada," "doll," or "ball" by 9 to 11 months of age, but lack of this criterion is not abnormal until 12 months. In this study, of sixty-five cerebral palsied children studied, 11 per cent said single words by 9 months, 15 per cent by 10 months, while 74 per cent were delayed beyond the 12 month norm. The average age for the onset of this item was 27.1 months.

Stands Alone: The normal infant can usually stand alone by 12 months, and the late normal limit is 13 months. In this study, of forty-three cerebral palsied children studied, 11 per cent stood alone by 12 months, 2 per cent by 13 months, and 86 per cent did not stand alone until after this period. The average age of standing alone was 27.5 months.

Walks Alone: The normal infant can walk alone between 12 and 15 months of age, while not walking alone until after 18 months must be regarded as abnormal. In this study, of fifty-seven cerebral palsied children studied, 7 per cent walked alone by 15 months, 16 per cent by 18 months, while 77 per cent walked alone only after 18 months. The average age cerebral palsied children

walked by themselves was 32.9 months.

Speech (2- or 3-Word Sentences): The normal infant can speak two- and three-word sentences ("Want bell," "Me go out") by 24 months, although speech is not considered seriously delayed until after 30 months. In this study, of thirty-nine cerebral palsied children studied, 31 per cent talked in sentences by 24 months, 23 per cent by 30 months, while 46 per cent did not talk in sentences until after 30 months. The average age for this development of this item was 37.4 months.

These data are summarized in Table I.

Average Age: The average age of appearance of the developmental items in cerebral palsied children was computed and compared with norms. There was a large difference between normal development and that of cerebral palsied children in every in-

TABLE I. DISTRIBUTION OF CEREBRAL PALSIED CHILDREN ACHIEVING MATURITY OF SPECIFIC DEVELOPMENTAL ITEMS

DEVELOPMENTAL ITEMS	NORMAL %	LATE NORMAL %	ABNORMAL %	NEVER %	TOTAL NO. CASES
Head control	14	18	68	–	74
Reaches	3	0	86	11	28
Sits without support	15	14	71	–	73
Crawls	0	2	37	61	54
Prehension	56	0	44	–	16
Speech, single words	11	15	74		65
Stands alone	11	2	86		43
Walks alone	7	16	77		57
Speech, sentences	31	23	46		39

TABLE II. AVERAGE AGE OF APPEARANCE OF DEVELOPMENTAL ITEMS IN CEREBRAL PALSIED CHILDREN

AGE IN MONTHS (NORMAL TO LATE NORMAL DEVELOPMENT)*	DEVELOPMENTAL ITEM	AVERAGE AGE OF APPEARANCE IN C.P. (AGE IN MO.)	DATA AVAILABLE NO. OF CASES IN THIS STUDY	AV. DIFF. BETWEEN LATE NORMAL AND C.P. (MO.)
1-3	Head erect from prone	12.4	74	9.4
3-5	Reaching	14.5	28	9.5
8-10	Sitting without support	20.4	73	10.4
7-8	Crawling	26.4	21†	18.4
9-11	Prehension	17.2	16	6.2
9-12	Single words	27.1	65	15.1
12-13	Stand alone	27.5	43	14.5
12-18	Walk alone	32.9	57	14.9
24-30	2- or 3-word sentences	37.4	39	7.9

*Based on Gesell's Norms, in Gesell, A., et al., The First Five Years of Life, New York, 1940, Harper & Bros.

†Thirty-three other cerebral palsied subjects never crawled.

TABLE III. RELATIONSHIP BETWEEN LEVEL OF INTELLIGENCE AND AGE OF ONSET OF SPEAKING TWO- OR THREE-WORD SENTENCES (N—36)

AGE OF SPEAKING TWO- OR THREE-WORD SENTENCES	INTELLIGENCE		
	BELOW 80	ABOVE 80	TOTAL
Below 29 mo.	2	12	14
Above 29 mo.	18	4	22
	20	16	36

$X^2 - 15.9$
$P > .001$

stance, with differences ranging from 6.2 to 18.4 months in delay. These data are summarized in Table II.

Developmental Chart.—From the above information, a chart has been devised which can be utilized as a diagnostic aid in general office practice (Chart 1). One additional developmental item, the tonic neck reflex, was included in the chart because it is easily observed in office practice.

gence tests as part of the evaluation for treatment at the Meeting Street School. A significant difference was found between those children who spoke sentences before 30 months of age and those who spoke after 30 months, in that those who did not speak in sentences until after 30 months were later found to be retarded in intelligence at the borderline range or below (Table III).

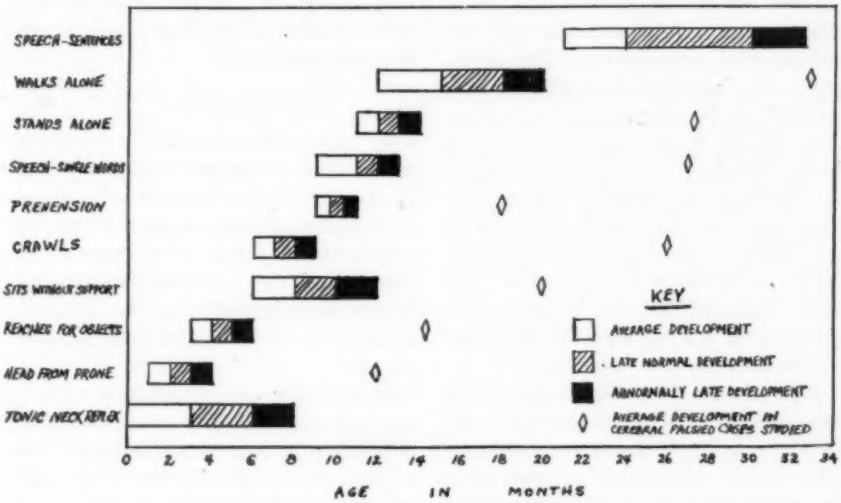

Chart 1.—Normal age of development as compared with average age of development of 100 cerebral palsied children.

Development and Intelligence.—An attempt was made to correlate developmental maturity and level of intelligence. The only developmental item which could be used to predict the intellectual level in the cerebral palsied children was age of onset of speaking two- or three-word sentences.*

Of the thirty-nine children about whom reliable speech information was available, thirty-six later had intelli-

*Thirty-nine children were able to make speech sounds and words, but not all thirty-nine had the mental ability to organize words into sentences.

DISCUSSION

The presentation of these data lends further emphasis to the importance of developmental deviations from normal early in life.

Although it would seem obvious that a cerebral palsied child would be slow in developmental progress, this does not invariably hold true in practice. An infant may be bright, alert, move all his extremities, yet have minimal or varying signs of neuromotor dysfunction, or both. For this reason, it is not unusual for many

mild cases to go undetected until later in childhood. However, this study emphasizes that 68 per cent or more of the cases were delayed in development very early in life.

Although there are exceptions to the rule, the chances for serious prognosis are increased particularly when several items are delayed beyond the late normal range. These delays are not specific for cerebral palsy, of course, but can apply to other conditions which are associated with developmental retardation. The developmental chart has been utilized successfully in lending support to a diagnosis which is suspected but is held back since the infant "looks so bright" or "appears so active." These reactions are not uncommonly found in minimally to moderately damaged infants. Reference to the chart will help minimize failures in early recognition of a syndrome which seems obvious one or two years later.

Abnormally late development in speaking in two- or three-word sentences has been shown to correlate with mental retardation as determined by psychologic tests. There was no other obvious correlation with other developmental items. However, a prediction about intelligence is not justified if a cerebral palsied child speaks in sentences at the usual time, since the results indicate that intelligence in such a case may fall into any category. In other words, a child who speaks sentences at the usual time may or may not be retarded, but if speaking sentences is delayed beyond 30 months there is great likelihood that the child will be retarded at the borderline level of intelligence or below.

The relationship between onset of speaking sentences and intellectual level will be a helpful diagnostic criterion of intelligence if it statistically holds true in a larger series of cases in other groups. An urgent need in cerebral palsy is a method of evaluating early those who are capable of benefiting from a well-rounded training program.

SUMMARY

1. The developmental histories of 100 cerebral palsied children were analyzed. Of the developmental items investigated, important deviations from normal were found in a majority of cases as early as 3 months of age. Deviations continued to be large in a majority of the cases until 3 years of age.

2. A chart which portrays normal, late normal, and abnormal stages of achieving developmental maturity has been found helpful in the early diagnosis of cerebral palsy.

3. A possible correlation between age of onset in speaking two- or three-word sentences and intellectual function is suggested by the data.

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EPIDEMIC DIARRHEA OF INFANCY

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BOTH in the United States[1] and England[2] the syndrome known as epidemic diarrhea of the newborn has been regarded as an infection limited to the neonatal period. In general, transmission to older infants and adults has not been considered a significant aspect of its epidemiology and has been ignored in preventive programs. From a broad epidemiological point of view it is difficult to conceive of an infection so specific as to confine itself entirely to hosts in the first four or six weeks of life. Such a disease would not be likely to succeed in self-propagation and would tend to die out with the passage of time.

Recent experience with epidemic diarrhea has demonstrated a tendency for the infection to appear simultaneously in different hospital nurseries,[3, 4] and several epidemiological studies have directed attention to the widespread prevalence of diarrheal disease in the community at large when outbreaks appeared in hospitals.[5, 6] Pediatricians have noted the spread of diarrheal disease not only in nurseries but also in pediatric wards and from them to child-caring institutions and private homes.[7] Because of these observations the question naturally arises as to whether the agent or agents responsible for epidemic diarrhea of the newborn also provoke the same disease among older children and in the community at large.

During the winter of 1946-1947, there was high incidence of nausea, vomiting, and diarrhea of unknown cause in the metropolitan Boston area.[6] Cases were noted by physicians in the community, in general hospitals, and in mental hospitals. Simultaneously, an outbreak of epidemic diarrhea of the newborn appeared in a large general hospital. It is the purpose of this study to record the epidemiological findings observed in this hospital and in other hospitals in the area, where newborn infants became ill with diarrhea.

The course of this epidemic is shown graphically in Fig. 1. It will be noted that the first cases occurred in the pediatric ward among infants aged 2 months to 1 year. Two such cases were admitted to the pediatric ward and both infants died. During the second week of December, five infants in the same ward developed diarrheal disease as a cross-infection. Each one of these infants had been admitted to the ward for some other reason. Subsequently, eight more infants with diarrheal disease were admitted to the ward, and five additional cases occurred as cross-infections, one of which was fatal.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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The newborn nurseries, which in this hospital were located in a separate building, remained free of the infection until late in December at which time four cases occurred in the premature nursery and a single case in the full-term nursery. The following week, six more cases occurred among premature infants and two among full-term infants. In spite of the fact that admissions were discontinued, cases continued to occur among infants as a result of previous exposure in both nurseries. A total of sixteen premature infants developed the infection, six of whom died. A single death occurred among ten full-term infants.

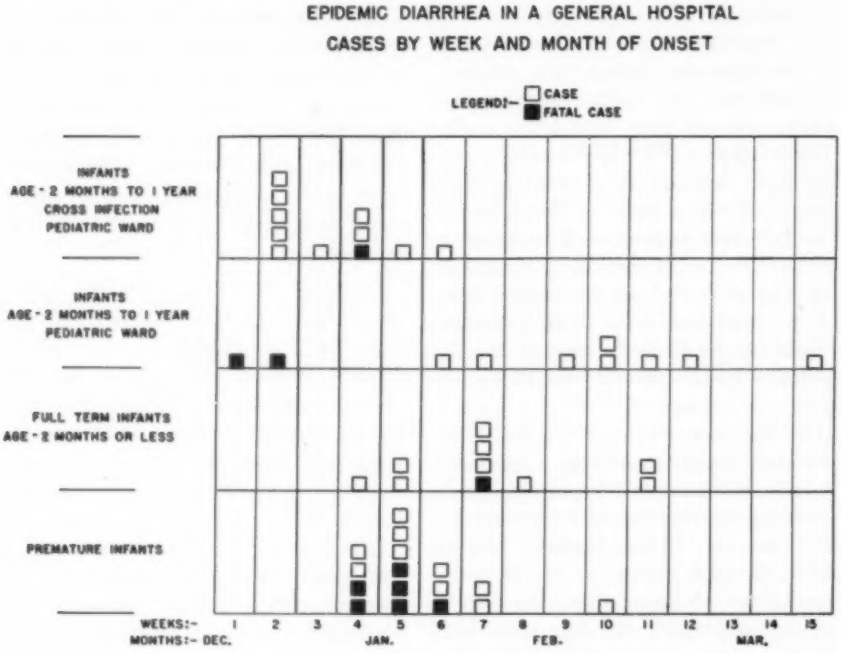
EPIDEMIC DIARRHEA IN A GENERAL HOSPITAL
CASES BY WEEK AND MONTH OF ONSET
LEGEND:- CASE
FATAL CASE
INFANTS
AGE - 2 MONTHS TO 1 YEAR
CROSS INFECTION
PEDIATRIC WARD
INFANTS
AGE - 2 MONTHS TO 1 YEAR
PEDIATRIC WARD
FULL TERM INFANTS
AGE - 2 MONTHS OR LESS
PREMATURE INFANTS
WEEKS:- 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
MONTHS:- DEC. JAN. FEB. MAR.

Fig. 1.

There was no exchange of nursing personnel between the nursery for newborn infants and the pediatric ward either before or after the outbreak. The only association between nurses of these sections of the hospital was in the nursing home before and after working hours. The same house officers and physicians, however, took care of patients on the pediatric ward and in the newborn nursery. Although there had been some cases of diarrheal disease among hospital personnel, no history of such infection could be elicited from nurses assigned to either the pediatric or newborn nurseries.

An attempt was made at this time to see whether diarrheal disease was present in other nurseries in the metropolitan area. Arrangement was made with three hospitals to supply

information concerning admissions of newborn infants with diarrhea. From these and other sources, it was learned that diarrheal disease among newborn infants had occured in five other hospitals in this area. Fig. 2 indicates that twenty-nine cases occurred in the nurseries of hospital A with nine fatalities, seven cases in hospital B with no deaths, twenty-two cases in hospital C with five deaths, six cases in hospital D with one death, and seven cases in hospital E with no deaths. All of these outbreaks occurred between November, 1946, and May, 1947, the same period of time when diarrheal disease was prevalent throughout this area. All of these later outbreaks occurred among newborn infants. Several infants were readmitted to the pediatric ward from their homes for diarrhea which developed soon after discharge from the full-term or premature nurseries.

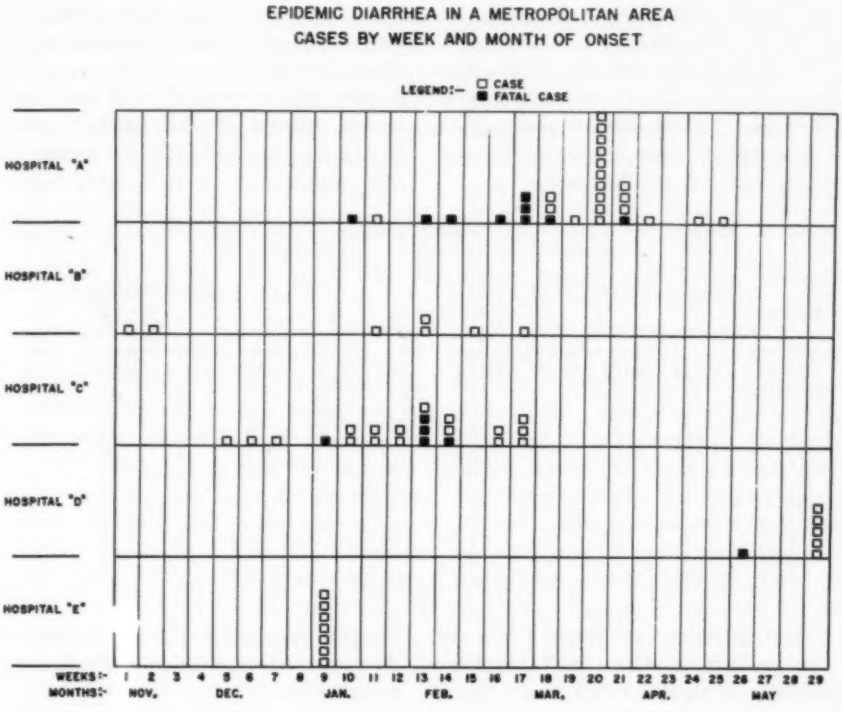
EPIDEMIC DIARRHEA IN A METROPOLITAN AREA
CASES BY WEEK AND MONTH OF ONSET
LEGEND:– CASE
FATAL CASE
HOSPITAL "A"
HOSPITAL "B"
HOSPITAL "C"
HOSPITAL "D"
HOSPITAL "E"
WEEKS:–
MONTHS:–
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
NOV. DEC. JAN. FEB. MAR. APR. MAY

Fig. 2.

SOME CLINICAL ASPECTS

The illness was generally febrile at some stage during its course. The temperature at time of admission was of little prognostic value. Fever was higher among the older infants, both among survival and fatal cases.

The white blood count was of little prognostic value. It was, in general, above 10,000 per cubic millimeter soon after admission and frequently rose

above 20,000. That these counts were not the result of dehydration was inferred from failure to observe corresponding elevations of red blood cells and hemoglobin percentages. The differential white blood count changed little with increase in the total count. The mean lymphocyte percentage for survivals was 49.3, for deaths 44.0. The mean percentage of neutrophiles for survivals was 42.2, for deaths 40.0. The mean percentage of eosinophilic polymorphonuclear leucocytes for survivals was 4.6, for deaths 2.5.

onset. It must be borne in mind that health authorities had warned parents as to exposure and the need for early treatment.

Stool cultures of seventeen patients were negative for organisms of the salmonella dysentery groups. In the eight instances where other organisms were reported, *E. coli* occurred seven times, and *S. aureus, S. albus,* and *S. fecalis* one time each. Nose and throat cultures of nine patients grew *S. albus* in six instances, *S. aureus* in five, diptheroids in four, and, infre-

TABLE I. EPIDEMIC DIARRHEA IN SIX GENERAL HOSPITALS—DURATION OF ILLNESS IN WEEKS ACCORDING TO AGE AND TYPE OF TREATMENT

DURATION OF ILLNESS (WEEKS)	AGE LESS THAN 1 MONTH					AGE 1 MONTH OR MORE				
	TOTAL	PENICILLIN	SULFONAMIDES	PENICILLIN AND SULFONAMIDES	SUPPORTIVE	TOTAL	PENICILLIN	SULFONAMIDES	PENICILLIN AND SULFONAMIDES	SUPPORTIVE
Survivals	24	8	1	11	4	24	8	1	11	4
0–	6	3	1	–	2	10	3	1	5	1
1–	7	3	–	2	2	10	4	–	3	3
2–	6	–	–	6	–	3	1	–	2	–
3+	5	2	–	3	–	1	–	–	1	–
Deaths	7	2	1	3	1	7	–	1	6	–
0–	2	2	–	–	–	3	–	–	3	–
1–	2	–	1	1	–	2	–	1	1	–
2–	1	–	–	1	–	1	–	–	1	–
3+	2	–	–	1	1	1	–	–	1	–

The duration of illness for sixty-two patients is shown in Table I, according to age at onset and type of treatment. Penicillin, sulfonamides, and their combination apparently had no marked effect in shortening the mean length of illness, 1.8 weeks, or in reducing the percentage of deaths. When the cases were ranked in order of severity from early recovery (less severe) to early death (most severe), no statistically significant differences were apparent, comparing infants whose onset of illness was at home with those whose onset was in the hospital, and comparing infants older or younger than 1 month at time of

quently, pneumococci, *H. influenzae, B. pyocyaneus,* and nonhemolytic streptococci.

Of particular interest, from the standpoint of early recognition, was the unexplained loss of weight in certain premature infants from two to six days before discovery of diarrhea.

DISCUSSION

Cummings[6] reported a series of outbreaks in a newborn nursery in Washington, D. C., in 2-day-old infants of mothers convalescent from "contact diarrhea" which was prevalent in the hospital vicinity. Abramson and Fuerst[7] reported an outbreak in a ma-

ternity service in New York City that spread to the nursery and from there to a child caring institution and to private homes. In the present instance, the illness was introduced from the community to a pediatric service of a large general hospital and spread to the premature and newborn nurseries. In each of these outbreaks the cause was not identifiable although clearly communicable, and the clinical and epidemiological patterns were those of epidemics from which Light and Hodes[8] were able to demonstrate the presence of filtrable agent in the stools which was pathogenic for calves. Reimann and associates[9] and Gordon and collaborators[10, 11] have obtained filtrable agents from the stools and upper respiratory secretions of adults with similar disease which produced illness in human volunteers in successive passages.

The incubation period has been estimated to be from one to twenty-one days, usually two days, both in infants[6, 7] and in adults.[12] Although the clinical descriptions are similar, the severity varies from outbreak, to outbreak, as would be expected. Cummings[6] reported a fatality rate of 3 per cent in the newborn nursery; Abramson and Fuerst[7] a rate of zero per cent. In the present series of outbreaks the fatality rate was 21.4 per cent. This rate may be compared to that observed concomitantly in occupants of a mental hospital building for the aged and infirm, namely 33 per cent.[3] In infants with a severe course, rectal temperatures and leucocyte counts are higher than are usually encountered among infants, youths, and adults.

It is not presumed that this fatality rate is a true picture of the expectation of death due to this disease, for the patients reported were either in a hospital when taken ill and therefore presumably not in robust health, or were probably the more alarmingly ill of the affected children in the general population. The total exposed and the total ill are not known. However, the evidence indicates that epidemic diarrhea of unknown etiology is not always a mild disease among the very young, the very old, and the infirm. Furthermore, fever and leucocytosis were not found to be dependable criteria for prognostication.

Observers are becoming increasingly impressed with the fact that diarrheal disease is difficult to control even under the best conditions. Unfortunately, there has been a tendency in this country to stress the importance of the disease among the newborn and to underestimate its significance among older infants. Hospitals that are paying more and more attention to techniques in newborn nurseries sometimes forget that cross-infections occur among older children. Individual techniques advocated for the newborn nurseries should also be employed in the pediatric ward.

The inability to reveal the etiological agent by laboratory methods should not discourage epidemiological studies in establishing modes of transmission and breaking chains of spread. It will be recalled that the epidemiology of such diseases as typhoid fever and cholera were established long before their respective causative agents were brought to light.

It is not unlikely that when the etiology of this disease has been definitely established, the difficulty in control will continue to be a problem. Subclinical and mild infection may

play an important part in the transmission of the disease from adults to infants, and for this reason it may always be a potential threat in newborn nurseries. It is not likely that first or second cases can be prevented in any situation, but a great deal can be done in preventing spread.

SUMMARY AND CONCLUSION

The experience of six hospitals with epidemic diarrhea of unknown cause among infants, at a time when the disorder was prevalent in mental hospitals and the community at large in the Boston metropolitan area, has been presented. It confirms the reports of others, that the illness is not limited to newborn infants, but may affect older children and occur among adults in the community.

Epidemic diarrhea among infants and adults is a communicable disease of unknown cause, generally mild, but occasionally severe in its manifestations among the very young, the very old, and the infirm. Its appearance in hospital nurseries and pediatric wards may be anticipated when it is prevalent in the community. Control measures are those which are applicable to other diseases disseminated by personal contact.

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THE TECHNIQUE OF PNEUMOENCEPHALOGRAPHY IN CHILDREN: COMPARATIVE RESULTS WITH AIR AND OXYGEN INJECTION

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PNEUMOENCEPHALOGRAPHY is widely used in the diagnosis of cerebral disorders in children as well as in adults, and a review of the special situation in children should be of interest. There are very definite limitations to the value of this diagnostic procedure, and on the whole it contributes more to neurosurgical than to neurological diagnosis.[1]

Pneumoencephalography is a safe procedure. The death rate is practically nil. There were no deaths in the 500 cases reported by us.[1] The most serious complication reported so far in the literature was detailed in the article by Smith and Crothers[2] where subdural air was followed by subdural fluid in 10 to 15 per cent of pneumoencephalograms in children which delayed the recovery. This is much more likely to occur in children under 2 years of age. We have not seen this complication, possibly because we do few pneumoencephalograms on very young children and possibly also due to the fact that we use oxygen instead of air as the injected gas.

There are two separate techniques in pneumoencephalography: (1) the technique of injection of the gas, and (2) the technique of the reading of the films. The first is the more important to the patient and the second to the doctor. This is not the place to go into the reading of the films. That is the function of the roentgenologist. The best of technical encephalography may be entirely useless unless the films can be read by a roentgenologist who has had wide experience with pneumoencephalographic films and is able to appreciate and understand all that he sees. No x-ray is any better than the man who reads the film.

The procedure of pneumoencephalography is safe but frequently very painful. We have directed our interest toward reducing the pain and shortening the period of recovery after the test. The early pneumoencephalograms were done with the injection of air into the lumbar subarachnoid space. We believe that even today air is the most commonly used injection gas. We used air at first, but following the work of Davidoff and Dyke,[3] we abandoned the use of air and ever since have been using oxygen. Other authors have suggested the use of other gasses but, as these are frequently difficult to obtain, we have restricted ourselves to oxygen which has been most satisfactory.

Our material consisted of 300 children on whom pneumoencephalograms were performed—200 in whom air was used (Group I) and 100 with oxygen (Group II). The age distribution of the two groups was similar, varying from a few months to 14 years. The

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diagnoses in each group are given in percentages in Table I. The amount of gas used was comparatively the same in both groups. Only the type of gas and the preoperative and postoperative medication varied.

Table I. Percentage Distribution of Diagnostic Groups in the Two Series

	CONVULSIVE STATES	POST-TRAUMATIC SYNDROME	INFECTIOUS DISEASES OF C. N. S.	NEOPLASM OF BRAIN	MENTAL RETARDATION	DEVELOPMENTAL DEFECTS	MISCELLANEOUS
Group I (Air)	55	7.5	5	1	9	8	14.5
Group II (Oxygen)	68	3	2	5	4	12	6

Bohn[4] found that the duration of the reaction to encephalography depended on the amount of gas used relative to the size of the ventricles. In the two present series, the percentage of reactions and the duration of symptoms increased as the amount of air or oxygen was increased. Of particular interest is the striking contrast Bohn noted between a group of patients receiving no premedication before encephalography and a group receiving morphine sulfate alone. In the former there were cardiorespiratory depressions in 21 per cent of the cases, whereas in the latter there were 43 per cent of cases manifesting this reaction. We feel on the basis of our later experience that the use of morphine as premedication in Group I caused the postencephalographic course to be more stormy and we have therefore not used it since 1935. Scott[5] claimed amelioration of symptoms both during and after encephalography by the use of atropine administered hypodermically fifteen minutes before the injection of air.

Table II gives a summary of the postencephalographic symptoms in our two groups and shows the very great advantage of oxygen over air. The time in which the children got out of bed demonstrates this probably better than anything else. These children were kept in bed so long as they preferred to lie down. When it was no longer possible to keep them lying and they insisted in sitting up or standing in the crib they were permitted to get up and remain up so long as they were symptom free.

PROCEDURE

The night preceding encephalography the patient is given an enema and fluids are forced until midnight. In Group I (air) premedication consisted of morphine or occasionally atropine and morphine in average doses for the age of the patient. This was given forty-five minutes before the gas injection. In Group II (oxygen) atropine and codeine* were used routinely as preoperative medication. Avertin anesthesia (approximately 100 mg. per kilogram) was used in almost every case, occasionally supplemented by ether.

After the patient is under the influence of Avertin, he is brought to

*The dosage commonly used for the premedication is as follows:

Age	*Atropine (Gm.)*	*Codeine (Gm.)*
6 mo.	0.00006	0.005
1 yr.	0.0001	0.008
2 yr.	0.0002	0.008
5 yr.	0.0003	0.015
8 yr.	0.0004	0.03
10 yr.	0.0006	0.06
12 yr.	0.0006	0.06

TABLE II. POSTENCEPHALOGRAPHIC SYMPTOMS WITH AIR AND OXYGEN
(Degrees of severity of headache and vomiting are indicated by plus signs.)

	ASYMPTOMATIC (%)		HEADACHES (%)					VOMITING (%)					TEMPERATURE (%)				SHOCK, IRREGULAR PULSE, TACHYCARDIA (%)		OUT OF BED WITHOUT SYMPTOMS (%)	
			AIR			OXYGEN		AIR			OXYGEN		AIR		OXYGEN					
	AIR	OXYGEN	+	++	+++	+	++	+	++	+++	+	++	+++	100-102	102+	100-102	102+	AIR	OXYGEN	AIR	OXYGEN
1st 12 hours	3.5	9	37.5	2.5	2	36	3.7	37.5	10.5	4	24	9	1	55	22	55	17	10	6		
2nd 12 hours	13	25	52.5	11.5	1	40	1.5	26.5	3		4	1		40.5	4.5	45	2				
2nd 24 hours	21	42	49	8	1	44	1	12.5	1		6	1		24	2.5	6	1				
3rd 24 hours	50	83	20.5	2.5		8	0	7.5	0.5		1	1		15.5	3	1	2			15	27
4th 24 hours	86	97	3.5	0.5		0	0	1	0		0	0		0	0	0	0			67	98

the x-ray department and seated on a bench with the forehead resting against a vertical Potter-Bucky diaphragm. The encephalographic technique employed is that described by Potter-Bucky diaphragm. The thighs are fastened to the bench. These simple means of support are found to be adequate for children in our age group.

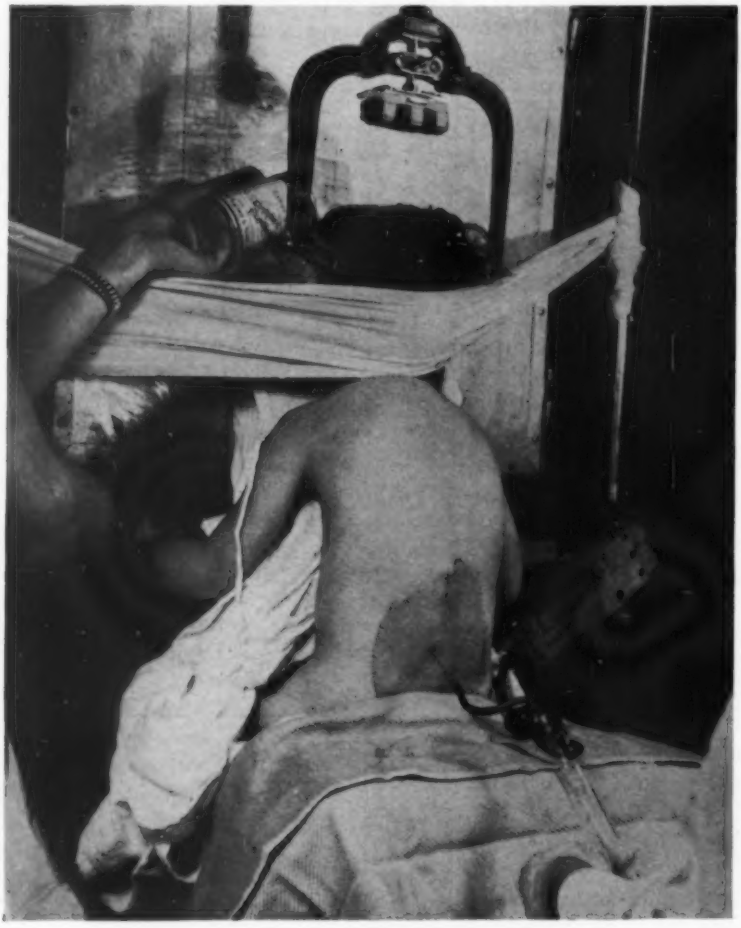

Fig. 1.—Child in position for pneumoencephalography.

Davidoff and Dyke.[3] The chin is supported by means of several pillows resting on the patient's lap and a sandbag placed directly underneath the chin. The head is strapped to the

With the child in position (Fig. 1) an 18 or 20 gauge spinal needle is introduced in the third or fourth lumbar interspace. A three-way valve is inserted in the needle, and rubber tub-

ing is connected to the arms of the valve. One of the rubber tubes is connected to a 20 c.c. syringe, the second to a rubber bag which in turn is attached to an oxygen cylinder, and the third to a collecting flask for spinal fluid.

An initial quantity of 10 c.c. of cerebrospinal fluid is removed and replaced with 5 c.c. gas. Thereafter, 5 c.c. fluid and 5 c.c. gas are alternately removed and injected. The fluid is allowed to flow out under its own pressure, and the injection of gas is at the rate of 5 c.c. in fifteen seconds.

The child's condition and vital signs are carefully observed and recorded during the procedure by the anesthetist.

After the 20 c.c. of gas have been injected, a single posteroanterior x-ray film is taken. This is developed immediately and the roentgenologist then advises how much more gas should be injected. This is usually an additional 40 or 50 c.c. If the ventricles appear enlarged, then a total of 85 to 120 c.c. of gas is injected. If the 20 c.c. film shows ventricular distortion suggestive of a neoplasm, the amount of gas injected is kept at a minimum. If the ventricles show no filling on the 20 c.c. film, then another 40 c.c. are injected. This rarely results in ventricular filling but the basal cisterns are frequently outlined. It should be emphasized that we never attempt to drain off the cerebrospinal fluid completely and that only on rare instances are more than 100 c.c. of gas injected. The examination always includes upright, lateral, and posteroanterior stereoscopic films.

The entire procedure, including the taking of seven sets of stereoscopic films, takes an average of forty minutes.

CONCLUSIONS

1. Because of the smoother postencephalographic course, oxygen is preferable to air as the gas to be used in pneumoencephalography.

2. Morphine leads to an increase in vomiting and respiratory difficulty following pneumoencephalography in children and its use is inadvisable.

3. Premedication consisting of atropine and codeine has been found satisfactory.

4. A technique of pneumoencephalography is outlined.

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ANOMALOUS ANAL PAPILLAE IN INFANTS AND CHILDREN

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A CONGENITAL anomaly of the anus in infants and children which has thus far eluded recognition is a condition in which one or more anal papillae have undergone abnormal development. This gives rise to a characteristic pattern of symptoms in early infancy. Except for a report[1] of this malformation by one of us (H. I. K.), the pediatric as well as proctologic literature does not reveal any mention of such a clinical entity. This is all the more surprising in view of the dramatic relief from symptoms secured by the surgical removal of these anomalous anal papillae.

Hitherto, their designation simply as anal tags has relegated them to a category of minor significance. Their abnormal embryologic development with the associated clinical manifestations has therefore received little attention from the medical profession. In a report by Mentzer[2] of seventy-five infants and children with anorectal disorders there is no reference to this type of mal-development responsible for symptoms associated with elimination. In about two-thirds of his patients the following conditions were present: fissure, cryptitis, prolapse, procidentia, abscess, and fistula. He noted that bleeding from hemorrhoids is very rare in the pediatric age group, there being only one in his series. The last (fifth) edition of Mitchell-Nelson's *Textbook of Pediatrics*[3] states: "Anomalies of the anus and rectum are comparatively uncommon, the incidence being approximately one per 8,000 births." The inclusion of the condition characterized by maldevelopment of anal papillae among the various anomalies of this region would markedly alter such a rare incidence. In pediatric practice, one of us (S. J. N.) has noted eight cases during a period of nine months; and a proctologist (H. I. K.) has observed fourteen cases over the past two and one-half years. Of the latter group, eight were previously reported.[1] Greater awareness of the presence of these abnormal anal papillae would help to elucidate some of the problems of painful defecation in infancy and childhood.

In the early embryo, the anal plate serves to separate the primitive hindgut from the proctodeum. An opening becomes apparent at about the fifth or sixth week. Significantly, the orifice is not developed as a circular stoma, but is produced by an invagination of irregular interdigitating epithelial-like folds, which are the anlage of the anal papillae and valves of Morgagni.

Normally, this invaginating process occurs in a cephalad direction so that the papillae and valves assume their usual location within the anal canal. However, with disturbance of the embryologic mechanism one or more of

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these papillae may develop in a reverse or caudad direction. In such circumstances exteriorization of the anomalous papillae occurs, and they subsequently appear as small, rounded, firm projections in the perianal region. Their shape may be polypoid or transversely cylindrical.

At the outset, symptoms may not necessarily be present in connection with these exteriorized papillae. However, irritating factors associated with defecation may lead to ulceration around their base. Severe pain with bowel movements may then ensue.

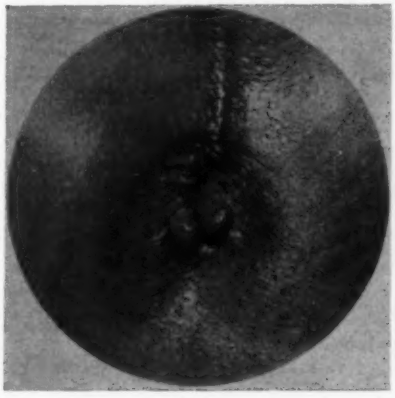

Fig. 1.—Case 6 demonstrates two anomalous anal papillae. At operation, ulceration was noted at the base of each.

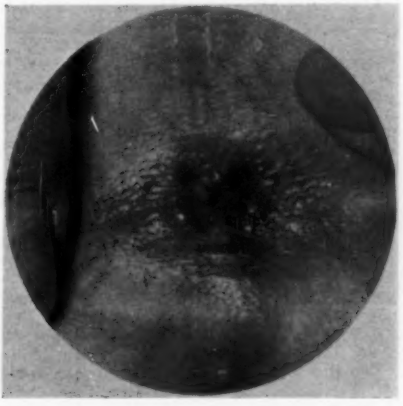

Fig. 2.—Case 9. An anomalous anal papilla can be see at the right anterior quadrant.

The crying of babies that is associated with the passage of stools is rarely ignored by parents. Their alertness in this respect should be shared by the examining physician in his efforts to determine the responsible factor. There is undoubtedly a group of diverse causes related to such disturbances in the young infant; and most of them can be readily eliminated by a careful inspection of the anus and the surrounding area. In many instances the mother herself has become aware of a small, fleshy tab in or near the anal opening. It frequently resembles an external hemorrhoid of an older individual. Occasionally, a drop of blood may appear on the stool. The pain during defecation may be so intense that the baby almost recoils from the act with paroxysms of severe screaming and crying.

Of the eight patients with this anomaly reported previously,[1] five were males and three females. Most of these were infants under 6 months of age. An additional group of fourteen cases is herewith reported in order to re-emphasize the clinical importance of this congenital anal anomaly. From Table I it is apparent that the ages of most of our patients were under 2 years. Eight of the fourteen patients were less than 1 year old. Except for the presence of anal tags noted by the mother, there were no symptoms of pain or bleeding in six patients. This group revealed a sex distribution of nine females and five males. Severe pain and discomfort during defecation

were the symptoms noted in five cases; bleeding with bowel movements in four. These symptoms were definite indications leading to surgical treatment. Seven patients were thus managed. Various other congenital anomalies were present in four cases. One patient had a younger sibling who also had been operated upon for the removal of an anomalous anal papilla. Constipation appeared in only two patients. Details of the surgical treatment have been described elsewhere by one of the authors (H. I. K.).[1]

anal papillae in the young baby will lead to more accurate and early diagnosis. The designation of any fleshy protrusion in the perianal area as merely that of an "anal tag" cannot be regarded as a final diagnostic entity. A neglectful attitude is thereby encouraged; and symptoms when apparent may become unnecessarily aggravated by delay in treatment. Operative removal of the anomalous papillae is, on occasion, almost an emergency measure. The relief is often dramatic. With the condition

TABLE I. CASES OF ANOMALOUS ANAL PAPILLAE CLASSIFIED ACCORDING TO AGE, SEX, SYMPTOMS, OTHER CONGENITAL ABNORMALITIES, AND TREATMENT

PATIENT	AGE	SEX	SYMPTOMS	OTHER CONGENITAL ABNORMALITIES	THERAPY
1. M. P.	3½ mo.	M	Extreme pain with defecation	Congenital heart; mongolism	Surgery
2. P. W.	3 yr.	F	Anal tag noted by mother. No symptoms	Vulvar adhesions; congenital heart murmur	None
3. R. B.	2 yr.	F	Anal tag noted by mother. No symptoms	None	None
4. J. C.	9 mo.	F	Severe pain with bowel elimination	None	Surgery
5. M. H.	10 mo.	F	Marked constipation	None	None
6. C. L.	7 mo.	M	Bleeding and painful bowel movements	None	Surgery
7. G. J.	15 mo.	F	Anal tags noted by mother. No symptoms	None	None
8. K. L.	11 mo.	F	Anal tags noted by mother. No symptoms	None	None
9. T. R.	4 mo.	M	Anal tags noted by mother	Telangiectasis of lip	Surgery
10. R. S.	3 yr.	M	Blood in stool; protrusion noted by mother	Pyloric stenosis at birth	Surgery
11. R. J.	8 mo.	F	Constipation; cried with bowel movements	None	None
12. C. W.	2 yr.	F	Blood and pain with bowel movements	None	Surgery
13. D. T.	9 yr.	F	Slight bleeding; protrusion in anal region	None Sister had had similar condition; was operated upon at age of 4 mo.	Surgery
14. C. H.	Newborn	M	No symptoms	None	None

COMMENT

In our combined groups totalling twenty-two cases it was apparent that this anal disorder is primarily concerned with the age group of early infancy. Awareness of the presence of such an anomalous development of untreated in those without symptoms the prognosis cannot be definitely ascertained.

SUMMARY

Attention is directed to the recognition of a clinical syndrome hitherto unreported in pediatric literature, con-

sisting of maldeveloped anal papillae which may be associated with painful or bleeding bowel evacuation in early infancy.

Fourteen cases of such anomalous anal papillae in infants and children are reported. Eight additional cases were previously recorded.

Early recognition of their presence is facilitated by a careful inspection of the anus and perianal area.

The extremely painful anal symptoms associated with ulceration of the base of the abnormal papillae are completely eliminated by surgical intervention.

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A MODERN CONCEPT OF BREAST FEEDING

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WITHIN the past few years considerable attention has once again been focused on the subject of breast feeding. At the present time, the general consensus of pediatric opinion is that breast feeding is of optimum advantage to the infant both physically and emotionally, and that it should be advised in all cases where a mother is physiologically capable of nursing.

Newspaper and magazine articles, as well as recent popular books on child care, have given the mothers of today the impression that breast feeding is essential to a close and satisfying relationship between mother and child.

However, careful study of our present knowledge concerning the physical and emotional welfare of infants definitely raises the question of the advisability of recommending breast feeding as a routine of pediatric procedure.

The so-called modern trend of idealizing and exalting breast feeding has not only caused confusion, but has, in numerous instances, brought forth feelings of inadequacy and even self-reproach in mothers who for one reason or another were unable to nurse their infants.

There are mothers who are physically incapable of nursing, although these are probably very few; there are working mothers who must place their infants on formula feeding immediately after birth. There are mothers who have no desire to nurse, who do not enjoy or may even abhor the idea of breast feeding. There are mothers who do not want to be tied down by breast feeding, others who would avoid any possibility of obesity during the nursing period, and still others whose husbands object to the idea.

These are the mothers who require and deserve further information on the degree of deprivation, if any, that their infants will suffer due to the lack of breast feeding. Are they really depriving their infants of an element essential to healthy growth and development both physically and emotionally?

It is true that today artificial formulas may be made in practically all respects similar to breast milk. A certain small amount of immune bodies is carried by breast milk but this is probably of little consequence when compared to the great number of immune bodies passed from the mother to her infant through the placenta.

Assuming, then, that the breast milk and the formula are approximately equal in all respects, are there superior values in the emotional development of the child that can be accrued only by means of breast feeding?

All agree that a warm relationship between mother and child is of fundamental importance, but is it necessarily true that this desirable warm

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relationship can always be attained or can be attained only through breast feeding? If a mother nurses against her desire, will nursing the child give her the happy experience it should? Will the child experience the warmth, comfort, and security at the breast of the mother who nurses against her will?

The answer is definitely negative. The desired relationship between the mother and child will be gained only when the breast feeding is an experience of mutual satisfaction both to the mother and the infant.

If, therefore, mutual satisfaction is the key to the question of whether to nurse or bottle-feed the baby, how are pediatricians and other physicians to determine which course to advise when the question arises?

For the purpose of clarity, one might roughly divide all new mothers into the following categories:

A. *Mothers who are anxious to nurse:* These mothers should receive every encouragement from obstetrician, pediatrician, and the nurses as well. Practically 100 per cent of these mothers are capable of nursing their infants if given the opportunity and the proper emotional support.

The attitude of physicians and nurses alike should be one of confidence and encouragement. The effect of emotional disturbances on the supply of breast milk is well recognized. A mother can be easily discouraged when told by nurses or physicians that her breasts are not secreting adequate amounts of milk.

B. *Those mothers who have no feeling pro or con but will nurse if it is considered best for the baby:* This group of mothers also should receive every encouragement to nurse. As a general rule, they soon find themselves enjoying the experience of breast feeding and need no further urging.

C. *Those mothers who would rather not nurse but will do so if it is considered best for the baby:* This is the most difficult group to advise for one must attempt to learn the degree of the mother's reaction against nursing. The subject of breast feeding should be calmly discussed and an effort made to remove any misconceptions. The decision should be made by the mother herself and she should receive every encouragement whatever method of feeding is chosen. If a mother chooses to try nursing, she should be given to understand that, if the experience is not a happy and satisfying one, the breast feeding will be discontinued.

D. *Those mothers who would rather not nurse due to fears of obesity, breast abscesses, and the fear of being tied down:* This group should not be encouraged to nurse for they would be doing so under a continued feeling of anxiety or frustration. The child will derive much more benefit from the bottle feeding given by a relaxed mother rather than from breast feeding given by a mother who is anxious about her own well-being.

E. *Those mothers who dislike and those who loathe the very thought of nursing:* This group should by no means be directed to nurse. They would only develop a feeling of antagonism for the child which could only prove detrimental to the mother-child relationship. The mothers who loathe the thought of breast feeding always have some deep-seated reason which cannot be removed by simple discussion or logic.

F. *Those mothers who cannot nurse because of economic situations where*

they are forced to work at such a distance or at such a time as to make breast feeding impossible: These mothers should be given to understand that their infants will not suffer physically or emotionally from receiving a formula feeding. This is the group of mothers who often develop feelings of guilt or inadequacy and are remorseful over situations which are beyond their control.

It has been mentioned that with encouragement and confidence the vast majority of American mothers could nurse their babies completely if they really desired to do so. However, the supply of breast milk is influenced greatly by emotional factors. The following case histories serve to illustrate this point.

CASE REPORTS

CASE 1 (J. C.).—This mother had every desire to nurse her baby. She was in a hospital where no encouragement was given in this direction. When, on the fifth day, her breasts were only secreting ½ to 1 ounce of milk at a feeding, she was advised to place the baby entirely on bottle. This was done almost immediately and the baby was taken off the breasts completely on the eighth day. Twelve days later, when the baby was home, she was first seen by the pediatrician. The mother expressed her unhappiness over her inability to nurse when she had such a deep desire to do so. On the suggestion of the pediatrician, the baby was returned to the breast and the breasts were stripped after each feeding. This infant was entirely on breast feeding within two weeks and was continued on the breast until 10 months of age.

CASE 2 (L. L.).—This mother was a well-known and extremely skillful child psychiatrist. She had every desire to nurse and was looking forward to the experience. Being a physician, she was given more privileges than the other mothers and was informed of the amount of milk obtained by the baby during each breast feeding. The infant started to take 1 ounce of breast milk on the fourth day, but the mother was quickly discouraged when on the fifth day the amount of breast milk was reported at ½ to ¾ ounce at each feeding. The nurses who reported the lack of breast milk were also very discouraging. Orders were immediately given that the mother was to receive no further information concerning the amount obtained by the baby at each feeding. She was told that the baby was doing well and was given the baby to nurse at more frequent intervals. The supply of breast milk immediately increased. In five days the child was entirely on breast feeding and in every way satisfied.

CASE 3 (V. F.).—This mother was very desirous of nursing but was discouraged by her physician who advised her that she was "no longer living in the horse and buggy age." After attempting breast feeding unsuccessfully for three days, she was advised by the nursery nurses as well as her obstetrician that further attempts were useless. On order of the obstetrician, the mother received stilbestrol the succeeding two days. The mother was extremely upset when first seen by the pediatrician. She felt completely "frustrated and inadequate." Further stilbestrol was discontinued, and the baby was once again brought to breast, but at three-hour intervals instead of four. The complemental feeding was held to a minimum both in quality and quantity. The breast milk immediately returned, and in seven days the complemental feedings were discontinued entirely.

These three cases are typical of many where a little encouragement has caused the increased secretion of breast milk and relieved the mothers of the feeling of inadequacy as well as anxiety.

It would appear, from a review of many cases, that in most instances the success or failure of breast feeding rests on the attitude of the mother as well as the support of her physician and nurses, rather than on the physical make-up of the mother. It is of extreme importance that this fact be recognized so that the success of breast feeding may be insured where it is felt that maximum benefit may be obtained through it.

There are a few mothers with inverted or very small nipples where the difficulty of nursing proves an unhappy experience for mothers and infants alike. In such cases, after a few days' trial at breast feeding, bottle feeding should be encouraged and prescribed. However, much of the difficulty by inverted or small nipples could be removed by prenatal care of the breasts. The problem of painful cracked nipples can usually be solved by local application and the temporary use of nipple shields.

Unfortunately, many obstetricians, in an effort to discourage nursing, emphasize to new mothers the possibility of painful breast abscesses as a direct result of this procedure. With simple precautions, breast abscesses are extremely infrequent, and today, when mastitis does appear, the early symptoms may in most instances be treated successfully by chemotherapy and antibiotics.

Briefly, it might be said that the nursing situation must be, without exception, one of mutual satisfaction. If it is not satisfactory to the mother, it cannot be completely satisfactory to the infant. This is a simple basic fact which must be understood not only by physicians and nurses, but also by husbands, grandparents, friends, and relatives.

SUMMARY

The decision as to the advisability of recommending breast feeding depends on whether or not nursing will be of the greatest mutual satisfaction to the mother and infant.

A mother who desires to nurse should be given every opportunity and encouragement.

Mothers who have no feeling pro or con but will nurse if it is considered best for the baby should be encouraged to nurse. As a rule, they will enjoy the experience and continue breast feeding.

Mothers who would rather not nurse but will do so if it is considered best for the baby should have all misconception removed by the physician. The final decision should be made by the mother herself.

Mothers who would rather not nurse due to fears of obesity, breast abscesses, and the fear of being tied down should not be encouraged to nurse, for they would be doing so under a continued feeling of anxiety and frustration.

Mothers who dislike and those who loathe the very thought of nursing should not breast-feed their babies.

Mothers who cannot nurse because of economic situations should receive reassurance that their infants will not suffer physically or emotionally from receiving formula feedings.

Whichever method a mother finally undertakes, there should be no sense of inadequacy or self-reproach, and she should receive every encouragement from her physician.

EMOTIONAL REACTIONS AND BEHAVIOR OF CHILDREN IN THE HOME

A Method of Study

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IN ANTICIPATION of an experimental study of the effects of anesthesia and tonsillectomy upon the behavior and emotional reactions of children, it seemed advisable to obtain definite information concerning the usual occurrence of certain traits and habits. An examination of the literature in related fields revealed only such facts as had been obtained on the basis of studies conducted in institutions. Since such observations would not be a valid base line for the experimental study, the following method was developed as a means of acquiring comparable information about the child in the home.

The difficulty of treating such material statistically is fully realized. Whether it can be done satisfactorily is open to question. On the other hand, if clinically observed phenomena in this field can be subjected to numerical analysis, the resulting evidence will have added value. This method is presented as a contribution to the development of such a technique.

SELECTION OF CASES

A certain public school was chosen for this investigation because it represented as nearly as possible a cross section of the local population. The plan of study was described to the school authorities and to the parent-teacher's association, with an invitation to the parents to participate in the project. The interested parents sent a letter indicating their willingness to talk with a social worker (R. W.). These letters were used by the worker as an introduction into the home. The 100 children in these families make up the group which was studied. This procedure proved to be a good one because the cooperation of both parents and school personnel was enthusiastic and intelligent.

The study was limited to school children from 5 through 7 years of age for two reasons. First, most children have had some separation experience before the age of 5 years, a matter of considerable importance in the proposed experimental project. Second, the upper limit was placed at such an age that, if the study should cover two or three years of the child's life, puberty problems would not cloud the picture.

COLLECTION OF DATA

A schedule of questions was prepared for use by the social case worker in her interview with the mothers. The purpose of the schedule and the interview was the collection of data concerning the child's behavior and family environment.

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The expenses of this study were defrayed by a grant from the Albany Society for the Advancement of Psychosomatic Medicine.

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General information included: the composition of the family, their economic and social status, the child's age and place in the family, and the usual methods of dealing with misbehavior. The intelligence quotient of the child was otained from school records.

Specific information about the child's behavior covered his daily activities in the home and as much as the mother could describe of his life at school and among his friends. Special attention was given to his ability and willingness to care for himself, his eating habits, his reaction to separation from home and to punishment. Inquiry was made regarding nightmares, temper outbursts, and mannerisms. The latter were considered under one category and included thumb-sucking, nail-biting, stuttering, bed-rocking, blinking, scratching, rubbing or picking at any part of the body.

Each interview took about two hours. Visits in any one neighborhood were scheduled in such a way that there would be a minimum of discussion between mothers and no feeling that information might be passed on by the case worker.

No mention was made of the experimental study nor were any questions included concerning anesthesia or tonsillectomy.

COMPILATION OF DATA

The information in the completed schedule was then transferred to code cards. Each category to be considered was given a code letter and each subdivision within the category was assigned a code number. Thus the code card became a comprehensive picture of the child's status, as represented by the mother's story.

It was then possible to determine (1) the occurrence of each of the factors under consideration, and (2) the relationship between any two categories. For example, it could be determined whether mannerisms were more or less common in only children than in the other groups; or whether tantrums occurred more frequently in children punished by deprivation than in those not so punished.

INTERPRETATION OF DATA

Judgments concerning emotions and reactions are difficult and of necessity reflections of the emotions or the objectivity of all the persons involved, (1) the mother, from whom the information is obtained, (2) the social worker who gathers the data, and (3) the persons who code the data. For the purpose of this study, the description of the child's behavior as given by the mother and reported by the social worker was accepted. The interpretation of data was the work of a committee of social workers, pediatricians, psychiatrists, and psychoanalysts.

To describe the child's reaction to absence from home and to discipline, an arbitrary set of terms was decided upon. A reaction was considered *positive* only if he were pleased by the experience or really accepting about it. The *negative* reactions were divided into two groups, aggressive and passive. The *negative-aggressive* group included those reactions which could be described by the words: hostile, angry, retaliatory, resentful, rebellious. The *negative-passive* reactions were those characterized as fearful, withdrawn, clinging.

In handling the factual material the difficulties were not so great but it was again necessary to make some

TABLE I

CATEGORY	REACTION	
	POSITIVE	NEGATIVE
Getting up in the morning	Gets up spontaneously	Requires urging
Dressing	Alone, with average speed	Requires help, urging
Interest in clothes	Expresses an interest	Does not
Care of clothes	Careful, clean, neat	Destructive, dirty
Eating	Eats spontaneously	Requires coaxing
Variety of foods	Eats variety	Does not
Enjoyment of meals	Enjoys meals	Does not
Bowel movements	Spontaneous	Requires laxatives
Going to school	Goes early or on time	Frequently late
Friends	Has a favorite friend	Has not
Punishment at school	No punishment	Punishment
Play	Active	Passive, solitary
Going to bed	Willingly, mild protest	Rebellious

TABLE II

CATEGORY	GROUP I	GROUP II	GROUP III
Nightmares	Frequent, severe	Occasional	None
Tempers	Violent	Severe, fleeting	Moderate
Mannerisms	Extreme, multiple	Single, moderate	None

TABLE III*

		PLACE				AGE			SOCIAL				ECONOMIC				TRAITS	
		1	2	3	4	5	6	7	I	II	III	IV	a	b	c	d	A	B
Place	1	21				9	5	7	1	6	10	4	2	16	3	0	8	13
	2		43			17	15	11	7	11	10	15	11	26	4	2	20	23
	3			16		6	5	5	3	7	5	1	2	11	2	1	11	5
	4				20	3	11	6	3	4	6	7	5	11	2	2	10	10
Age	5					35			5	11	11	8	9	22	3	1	18	17
	6						36		5	8	9	14	3	25	5	3	17	19
	7							29	4	9	11	5	8	17	3	1	14	15
Social	I								14				5	9	0	0	7	7
	II									28			6	21	1	0	15	13
	III										31		6	21	4	0	17	14
	IV											27	3	13	6	5	10	17
Economic	a												20				10	10
	b													64			36	28
	c														11		2	9
	d															5	1	4
																	49	51

Place 1—only child
2—oldest child
3—middle child
4—youngest child

Social I—nonskilled
II—skilled
III—business
IV—professional

Economic a—under $3,000
b—$3,000-$5,000
c—$5,000-$10,000
d—$10,000 and over

Traits A—Number of children with two or less negative traits each
B—Number of children with three or more negative traits each

*Arranged by Dr. Edgar A. Doll, Devereau Schools, Devon, Pa.

arbitrary decisions. Table I shows our method of classifying the material.

In certain of the categories it was necessary to divide the data into three groups (Table II).

ANALYSIS OF DATA

Table III demonstrates the use of a multiple reference table. With this arrangement of the data, correlation can be made between any two factors. For example, it can be seen that of the fourteen children in the families of nonskilled workers, only one is an only child; whereas, in the families of businessmen, ten of the thirty-one children fall in this category. Also, of the fifty-one children showing three or more negative characteristics, five are middle children (31 per cent of all middle children); whereas, thirteen are only children (61.9 per cent of all only children).

Table IV, showing the number of negative characteristics per child, groups them again according to place in the family, age, and economic and social status. Note the low figure which appears for the middle child as compared to the only child and also the shift toward the lower number of negative traits in the two lower income groups.

Table V presents data concerning the specific characteristics with the children divided according to place in the family. The only child shows a higher than average incidence in eight of the eleven negative traits. The middle child, who scores less than average in eight negative characteristics, shows more than twice the number of nightmares.

Table VI shows that where the groups are almost equal in number, no significant deviations occur according to age.

Data concerning the child in relation to the size of the family are to be dealt with in a later paper in which the material is presented from a sociologic point of view.

TABLE IV

		NUMBER OF NEGATIVE TRAITS									TOTAL NO. CHILDREN	AV. NEG. TRAITS PER CHILD
		0	1	2	3	4	5	6	7	8	100	2.8
Place	1	0	1	7	3	4	3	2	0	1	21	3.6
	2	2	7	11	8	6	4	4	1	0	43	3.0
	3	2	5	4	3	1	0	1	0	0	16	2.0
	4	2	3	5	6	3	1	0	0	0	20	2.4
Age	5	3	6	9	4	4	5	4	0	0	35	2.9
	6	2	4	11	9	5	1	2	1	1	36	2.9
	7	1	6	7	7	5	2	1	0	0	29	2.6
Social	I	1	3	3	6	1	0	0	0	0	14	2.2
	II	4	6	5	5	4	1	2	0	1	28	2.6
	III	0	4	13	4	4	3	3	0	0	31	2.9
	IV	1	3	6	5	5	4	2	1	0	27	3.5
Economic	a	2	4	4	4	3	1	2	0	0	20	2.7
	b	4	12	20	12	6	5	3	1	1	64	2.7
	c	0	0	2	3	4	0	2	0	0	11	3.7
	d	0	0	1	1	1	2	0	0	0	5	3.8

The deviations in all the tables are small and could be considered statistically significant only if they were found in an additional series of cases. The greatest departures from the average occur where the group is compara-

tively small; namely, the middle child group, the nonskilled worker group, and the two higher income groups. Where the groups are of similar size, as in the age groups, no real deviation occurs.

cerning in her observations of the mother. Obviously it devolves upon the interviewer to detect and evaluate such emotional difficulties on the part of the mother as might influence her picture of the child. An understand-

TABLE V

BEHAVIOR TRAIT	100 CASES	ONLY CHILD	OLDEST CHILD	MIDDLE CHILD	YOUNGEST CHILD
Negative reaction to separation*	56%	75%	52%	45%	50%
Does not get up spontaneously	31	33	32	18	35
Dresses only with help or urging	47	62	51	37	30
Destructive or dirty with clothes	25	25	25	25	25
Requires coaxing to eat	36	57	27	37	30
Does not enjoy meals	31	28	39	6	35
Violent temper	21	33	20	12.5	15
Severe or multiple mannerisms	31	33	37	12.5	35
Rebellious about going to bed	6	14	7	0	0
Severe nightmares	6	4.7	4.6	12.5	5
Lapses in toilet training	8	9.5	9.3	6	5

*These percentages are corrected to include only those children who have had a separation experience.

TABLE VI

BEHAVIOR TRAIT	100 CASES	5 YR.	6 YR.	7 YR.
Negative reaction to separation	56%	50%	50%	70%
Does not get up spontaneously	31	20	36	40
Dresses only with help or urging	47	49	50	44
Requires coaxing to eat	36	42.8	33	31
Destructive or dirty with clothes	25	25.7	30	17
Does not enjoy meals	31	37	27.7	27.5
Violent temper	21	28	16.6	17.9
Severe or multiple mannerisms	31	40	30.5	20.6
Rebellious about going to bed	6	2.8	8	6.9
Severe nightmares	6	5.7	8	3.4
Lapse in toilet training	8	8.5	11	3.4

EVALUATION OF METHOD

The value and the validity of our method lie in the qualifications of the persons engaged in gathering and interpreting the data. Two fundamental problems are to be met: securing accurate data and translating them into terms which can be codified.

The first of these problems involves the qualifications of the case worker. This person must be not only trained in the art of interviewing, but also experienced in work with children. In addition, she must be mature and dising and sympathetic person, with enough experience, can usually get a fairly accurate impression of the child from the mother, although she may need to test her impression by further questions, confirming or correcting it in accordance with additional information. When this is impossible, the interviewer can at least recognize the inaccuracy and the case can be omitted.

The problem of translating data into terms capable of codification requires knowledge and experience concerning

the behavior and emotional reactions of children. Considering the basic difficulty of expressing emotions in words, it is to be expected that there will be, at first, disagreement between any two interpreters as to which words to use. It would seem that the only practical procedure is to define the terms as clearly as possible, and agree on an arbitrary interpretation. This will mean, of course, that many of the finer gradaations of meaning in psychiatric terms will have to be sacrificed, but at least it provides a workable method, even though it is relatively crude.

The sorting and cross filing of code cards by symbols, and the tabulation of the data, is a technical task which can be done by any one familiar with simple mathematical processes.

The value of the method lies in the following features: (1) It goes directly to the mother for the facts concerning the child, and, presumably, she knows more about the child's behavior than anyone else. (2) It shows us the "normal" child in his accustomed and natural surroundings. (3) The code cards make possible any number of calculations and comparisons. The significance of conclusions based on such calculations increases, of course, with the number of cases studied.

SUMMARY

A method of study of behavior traits and emotional reactions in children in the home has been described. The merits and limitations of the procedure are pointed out. Its application in 100 cases is demonstrated and the resulting figures analyzed.

A CHART ON ERUPTION OF THE DECIDUOUS TEETH FOR THE PEDIATRICIAN'S OFFICE

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THE JOURNAL for December, 1950, includes a paper[3] dealing with dental questions that frequently are "asked the pediatrist." The writer of the paper states: "The most common query of a dental character that is directed to pediatricians is that concerning the eruption time of . . . teeth." To aid the pediatrician in formulating "answers" to such questions, a table of approximate "average ages of eruption" is reproduced. The limitations of this table are frankly acknowledged and the clinician is warned that "it is often misleading to apply average values to individual cases" since there exist "wide variations within a normal range."

It is the purpose of the present report to place in the hands of the pediatrician a more adequate compilation of information regarding the time and order of eruption for the deciduous dentition. In 1946, I assembled and synthesized the findings from twenty-two investigations on the age and sequence of eruption of deciduous teeth in North American children.[2] This synthesis took the form of "a series of statements" which attempted to "epitomize present knowledge of the problem."

Chart I has been constructed from my 1946 integration of North American research materials on deciduous eruption. The objective in construction was to arrange in a form convenient for clinical reference, as many of the practically useful composite results as could be displayed on one page.

It will be seen that the chart is captioned: Age and order of eruption for the deciduous dentition in North American white and Negro children. While the available materials on North American Negro children are not as plentiful as those for North American white children, it appears that the two racial groups do not differ appreciably in eruption of the deciduous teeth.[2]

One frequently reads or hears statements similar to the following: "In girls, teeth erupt earlier than in boys."[3] With particular reference to the deciduous dentition, such statements are incorrect. Investigative evidence shows conclusively that the teeth of the deciduous complement "tend to erupt earlier in males than in females."[2]

Chart I treats the deciduous dentition exclusively. Pediatricians desiring similarly comprehensive information for the eruption of the permanent dentition are referred to the excellent recent work of Dr. V. O. Hurme.[1]

From the School of Health and Physical Education, University of Oregon.

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CHART I

AGE AND ORDER OF ERUPTION FOR THE DECIDUOUS DENTITION IN NORTH AMERICAN WHITE AND NEGRO CHILDREN

*Age of Eruption of the First Deciduous Tooth**

Number of Subjects	Mean Postnatal Age	Zone for 98 per cent	Range
1,095	7.5 mo.†	4 to 12 mo.	0‡ to 16 mo.

*For about 95 per cent of infants the first tooth to erupt is a lower first incisor; occasionally, eruption begins with an upper first incisor, an upper second incisor, or a deciduous first molar.

†At age 6 months only one infant in three has any erupted teeth.

‡In rare instances, eruption of the deciduous dentition commences prior to birth. (For data on this problem, see Massler, M., and Savara, B. S.: J. PEDIAT. 36: 349, 1950.)

Number of Erupted Deciduous Teeth at Selected Ages§

Postnatal Age	Number of Subjects	Mean Number of Teeth	Zones for: 50 per cent	Zones for: 98 per cent	Range
9 mo.	670	3	2 to 5	0 to 8	0 to 12
12 mo.	700	6	4 to 8	1 to 11	0 to 20‖
18 mo.	500	13	10 to 14	6 to 18	4 to 20
24 mo	510	17	15 to 18	10 to 19	8 to 20

§The process of deciduous eruption is timed about two weeks earlier in the average male than in the average female.

‖The characteristic eruption sequence for the deciduous dentition is lower first incisors, upper first incisors, upper second incisors, lower second incisors, first molars (upper and lower), canines (upper and lower), lower second molars, upper second molars. Numerous individual variations occur, e.g., the third tooth to erupt is an upper second incisor in about 20 per cent of infants and a lower second incisor in about 5 per cent of infants.

Age at Which Eruption of the Deciduous Dentition is Completed¶

Number of Subjects	Mean Postnatal Age	Zone for 98 per cent	Range
226	28 mo.	18 to 36 mo.	10 to 38 mo.

¶The amount of time taken by different individuals in erupting the deciduous complement varies from less than nine months to thirty-five months; for over 90 per cent of children all twenty teeth erupt within time spans of eighteen to thirty months.

A NEW SUCKLING DEVICE FOR ARTIFICIAL INFANT FEEDING

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IT IS apparent that the bottle-nipple assemblies that are now available have many inadequacies. Physicians who care for infants see many babies each week who are suffering because of these inadequacies.

The quantity of milk that an infant receives from the present-day nipple depends mainly on the size of the holes in the nipple. If the perforations are too small the infant repeatedly receives an inadequate amount of milk, thus resulting in cyclic hunger, crying, and air-swallowing. On the other hand, if the holes are large enough, regardless of the infant's sucking, there is a constant flow of milk. This constant flow results in the mouth and pharynx being full of milk in both phases of the sucking-relaxation cycle and likewise contributes to air-swallowing and discomfort.

It will be shown why the functioning of the conventional nipple is unnatural and utilizes the infants sucking reflex in an inefficient manner. A new principle presented here shows how artificial feeding can be a more natural process.

DEVELOPMENT OF THE NEW PRINCIPLE

In an effort to improve the present infant nursing bottle, one logically turns to the functioning of the human breast. In tracing the lactiferous ducts from the nipple into the breast, an ampulla or lactiferous sinus is found just proximal to the nipple. The ducts again narrow and continue to the acinar structures. During lactation, milk is produced in the acini of the mammary gland and flows via the lactiferous ducts into the immediately available reservoirs, the lactiferous sinuses. On suckling the breast, the infant compresses the nipple and areolar area between the tongue and hard palate, thus compressing the lactiferous sinuses, and milk flows into the infant's mouth. There is an efficient flow of milk on suckling because there is a narrowed constriction behind the lactiferous sinus. Histologically, the lactiferous duct is made up of connective tissue fibers and longitudinal and circular elastic fibers. This histological make-up is no doubt of importance in the refilling of the lactiferous sinus following each emptying. If the lactiferous ducts become overly distended, they lose their tone, and the mother has troublesome leakage of milk.

In the preliminary planning of this new principle, the aim was to furnish a device which would offer to the small infant a method of artificial feeding which would enable him to obtain milk

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according more to his desire than to the size of the nipple perforations. Any mother or nurse who has had artificial feeding experience can tell you of her despairing efforts in maintaining the correct-sized perforations.

conventional baby bottle and nipple, one can immediately see the mechanical reason for its poor performance. As the infant compresses the nipple between the tongue and the hard palate the transmitted internal pressure

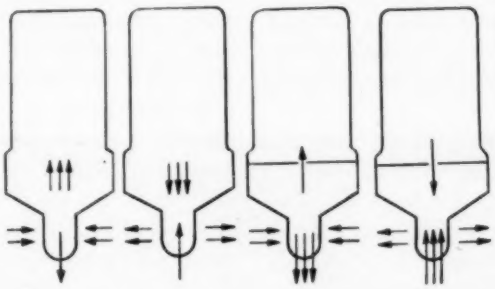

Fig. 1.—*A*, Compression of the conventional nipple results in an excessive upsurge of milk into the bottle. *B*, On expansion of the conventional nipple, the refilling is mainly from the bottle. *C* and *D* represent a constricting diaphragm containing a small orifice inserted between the nipple and bottle. The upsurge of milk into bottle on compression is now minimized and there is adequate flow of milk through the nipple perforations. Expansion, however, results in filling of the nipple with excessive air.

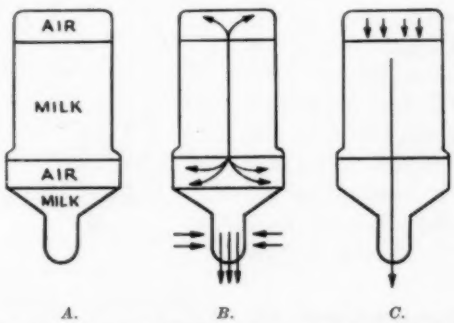

Fig. 2.—*A*, *B*, and *C* illustrate the failure of a constricting diaphragm. In *A* it is seen that the excessive intake of air on expansion results in the leveling off of the air above the milk in the nipple. On further compression of the nipple, the air is pumped into the space above the milk level, *B*. After a few minutes of nursing the excessive collection of air trapped above the milk forces the milk out in a constant stream, *C*.

Second, it was felt that a simple method was needed that would provide milk to the infant during sucking efforts and not flood the baby's mouth and pharynx during relaxation. In considering the inadequacies of the

results in an excessive flow of milk back into the bottle with only a small amount into the infant's mouth (Fig. 1 *A*). Therefore, the infant's sucking efforts are utilized inefficiently and the amount of milk obtained depends

mainly upon the size of the nipple perforations and gravity. If the holes are too small, hunger, crying, and air-swallowing result. If the holes are enlarged sufficiently, the infant will obtain adequate milk, but the flow will continue during relaxation as well as during the sucking phase of nursing. This constant flow frequently results in gagging, choking, regurgitation, and air-swallowing.

After considering the anatomy and functioning of the human breast, it was theorized that if a diaphragm with a small opening were placed between the bottle and nipple, the upsurge of milk into the bottle during compression would be significantly reduced and an efficient flow through the nipple perforations would result. Such a device was tried, and as was expected, an efficient flow was produced on compression (Fig. 1 *C*). However, it became apparent that this setup acted as a miniature air compressor, and after a few minutes of nursing the milk would flow from the bottle in a constant stream. This constant flow of milk is produced by the excessive air collected above the level of the milk (Fig. 2). Naturally, this is undesirable.

It was discovered that too much emphasis had been placed on compression of the nipple; expansion is also of great importance. As the nipple expands it must be filled with either milk from the bottle or air from the exterior. As is shown in Fig. 2, the simple constriction between the nipple and bottle is unsuccessful because excessive air is sucked into the nipple during expansion and is subsequently pumped into the space above the milk. If one attempts to enlarge the opening between the nipple and bottle in an effort to obtain a better flow of milk into the nipple on expansion, his efforts will be in vain. When the opening is enlarged sufficiently to satisfy this requirement, the original aim of an efficient flow of milk from the nipple on compression is defeated.

A mechanism is needed whereby there is only a small opening between the nipple and bottle on compression and a large opening on expansion. This needed mechanism is furnished by a simple check-valve device (Fig. 3). On compression, there is a minor upsurge of milk through a small relief orifice (Fig. 4) with the major flow into the infant's mouth. On expansion, the valve disk opens and a large opening is created between the nipple and bottle, thereby allowing the nipple to be filled freely from

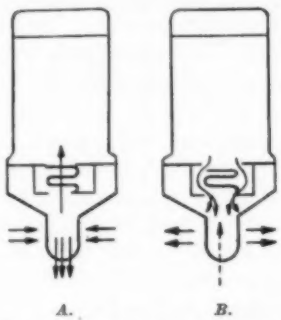

Fig. 3.—*A* and *B* show compression and expansion of the nipple with the new nursing adapter inserted. Compression results in a flow of milk identical to that shown in Fig. 1*A*. However, on expansion, the valve opens and there is free filling of the nipple from above. When the pressure in the nipple rises to that in the bottle, the valve will again close. Air needed above the milk level in bottle will enter through the nipple and ascend through the relief orifice shown in the valve disk (this will prevent the formation of a vacuum above the milk level).

above with milk. When the pressure in the nipple reaches that in the bottle, the spring again closes the valve disk. The minute relief orifice in the valve disk is an absolute necessity for without it air cannot enter the bottle and a negative pressure will develop above the level of the milk, and thus interfere with the flow of milk into the nipple.

ing, the valve opens momentarily (due to sudden decrease in pressure within the nipple) and milk flows into the nipple reservoir. After the first few suckles the nipple becomes filled, and with further compression, the pressure relationships that are shown in Fig. 3 result in an efficient flow of milk into the infant's mouth. The force and amount of this flow are directly pro-

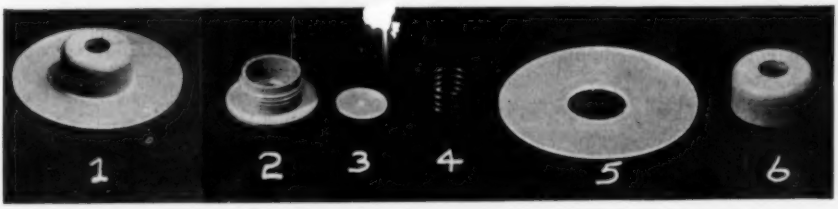

Fig. 4.—Nursing device showing component parts: 1, device assembled; 2, valve seat; 3, valve disk with relief orifice in its center; 4, valve spring; 5, diaphragm; 6, valve cap.

A simple flutter valve was also tried. This consisted of a valve disk which opened and closed wholly on a hydrostatic basis. This device was found to work unsatisfactorily and it was concluded that the spring is an essential part of the valve mechanism.

THE NEW NURSING CONTROL*

The final and most satisfactory device in fulfilling the initial aims is shown in detail in Fig. 4. This device is called a nursing control. With the insertion of this control between the nipple and bottle, two potential reservoirs are created; an immediately available reservoir, the nipple, and a large supply reservoir, the bottle. As the infant now compresses the nipple, the check-valve is closed; upon relax-

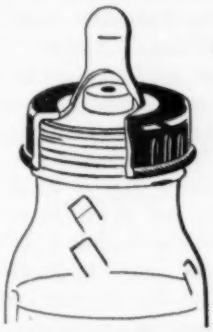

Fig. 5.—Nursing control as seen inserted in nipple bottle assembly.

portional to the efforts exerted by the infant. So as the baby nurses, sucking produces a smooth and adequate flow of milk, and with relaxation the valve opens allowing a continued supply in the nipple reservoir. Therefore, there is provided a mechanism whereby the infant receives milk according to the effort expended and only dur-

*Atatrol Nursing Control—Patent pending; inventor: Weldon Porter. Manufactured and distributed by the Atlas Medical Accessory Co., 1911 West Alabama, Houston 6, Texas.

ing the sucking phase (not during the relaxation phase). It is thought that the functioning of this device closely resembles that of the human breast.

In its present manufactured form, the new nursing control is made of materials (polyethylene, anodized aluminum, and stainless steel) which may be sterilized by boiling or autoclaving and which are nonreactive to water, orange juice, lactic acid, and milk. The component parts are simply detachable, which permits necessary cleansing. The nursing control fits the available screw cap baby bottles that are now on the market (Fig. 5).

UTILIZATION OF THE NEW PRINCIPLE

The most common condition for which the physician sees the infant during the first three months of life is a condition I choose to call the hunger-air syndrome. The symptoms which make up this syndrome are incessant crying, abdominal distention ("gassy"), spitting up, and loose mucoid stools (or at times constipation). To any physician seeing small babies, this constellation of symptoms is observed daily and often to the extent that he becomes haunted by the ever-present existence of this clinical problem. The etiology of this syndrome is primarily hunger. Rosamund[1] states that "hunger and colic are synonymous." This syndrome occurs in both the breast and artificially fed infant.

Hunger in the artificially fed baby is most commonly due to his unsuccessful attempts to obtain milk through inadequate nipple holes. The distention and "gassiness" are due to swallowed air. Many mothers and some physicians believe this gas is due to indigestion and fermentation. Marriot and Jeans[2] state the distention is more frequently due to air-swallowing than to gases of fermentation, since the latter are mainly carbon dioxide and are absorbed more rapidly than the swallowed air. They also state that the swallowed air is most commonly a result of underfeeding. Smith and LeWald[3] have shown roentgenologically that swallowed air accounts for gas in the large majority of cases. The regurgitation, and at times projectile vomiting, is due to the upward surge of eructated air. Underfeeding is a much more common cause of vomiting in infancy than overfeeding. The loose stools are due to hyperperistalsis, and constipation to the spasticity of the anal sphincters.

It is not intended to discuss breast versus artificial feeding. It is apparent that approximately 70 per cent of the infants born in this country are being entirely artificially fed by the age of one month. Whether this be good or bad it is an existing fact. In my opinion the most important etiological factor leading to the hunger-air syndrome is not the milk mixture, but rather the artificial nipple. Babies are seen daily who suckle literally for hours to obtain only 6 to 10 ounces of milk. Many of these babies can be helped merely by enlarging the nipple holes. However, in many instances when the holes are enlarged adequately the infant has difficulty in handling this constant unphysiological flow of milk. This constant flow is another big factor contributing to air-swallowing.

Many such infants have been treated during the past six months by insertion of the new nursing control into the nipple-bottle assembly. A representative case follows:

L. W., a white female, weighed 8 pounds, 2 ounces at birth and at the age of 2 weeks weighed 7 pounds, 12 ounces. She had done well on the breast until the age of 11 days at which time the breast milk supply markedly decreased and she became "hungry and gassy." She was placed on evaporated milk 1½:water 2½ complement. She continued to cry and to be distended with gas. At age 3 weeks the breasts "dried up," and she was begun on formula alone and was given an antispasmodic with continued crying and gassiness. By the age of 2 months she was still having the same difficulty in spite of change to homogenized milk and the addition of phenobarbital and solid feedings. At this age she was taking 2 to 4 ounces of homogenized milk each feeding. She was placed on the new nipple attachment, and in twenty-four hours she was sleeping "like a log" and taking 6 to 7 ounces each feeding. This improved condition continued and at the age of 4 months she weighed 13 pounds, 8 ounces. Her physical examination was negative throughout this period.

Feeding of newborn infants with lip and palate defects certainly offer a challenge in artificial feeding. It is felt that this new principle may be of great value in the feeding of many of these infants. The following case illustrates this well:

J. V., a white male, was seen for the first time at the age of 11 days. He weighed 8 pounds at birth and 7 pounds, 3 ounces at 11 days. He was found to have a double cleft palate, extremely deformed ears, and a meningocele in the occipital region. Feedings with medicine dropper, bottle-nipple, and Brecht feeder were all unsuccessful. The baby was crying, distended, and obviously hungry. He was hospitalized and fed by gavage for forty-eight hours with success. He was then placed on nipple and bottle again but could take only ½ to 1 ounce in a one-hour nursing period. At this time the new feeding attachment was added to bottle-nipple assembly, and the baby immediately started taking 4 ounces in a fifteen- to twenty-minute nursing period. His progress has since been good.

This new principle has been tried in both premature and full-term newborn infants with success. The value observed in its trial on premature infants has been particularly noteworthy. If the premature infant has a sucking reflex, he is enabled to obtain milk safely and with maximum efficiency. The utilization of this principle in artificial infant feeding in general has demonstrated it to be of apparent value. It is simple and logical and deserves further and thorough trial.

SUMMARY

A new principle in artificial infant feeding is presented. The basis of this principle is discussed and its advantages are shown diagrammatically. To fulfill the functioning of this principle, a simple device, operating on a check-valve mechanism, is used. This device is shown in photographs.

The utilization of this principle in infant feeding is discussed and illustrater by representative cases. Trial of this new principle in premature infants, full-term newborn infants, babies with the hunger-air syndrome, infants with lip and palate defects,

and normal infants has demonstrated evidence of its value.

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A SELF-LUBRICATING SYRINGE

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INTERNS and residents are disturbed frequently by syringes sticking when giving intravenous fluids and transfusions. The need for a nonsticking and smoother operating syringe has been recognized for some time.

A syringe has been devised to overcome the tendency to freeze the plunger in the barrel when transfusions or intravenous fluids are being given. A photograph of two models of the syringe is shown in Fig. 1.

The lining of the barrel has circular rows of small channels or semicuplike reservoirs grooved near the opening of the barrel, designed to contain either fluids similar to that being used in the syringe, or a lubricating fluid as glucose or physiological saline in the giving of transfusions.

To load the reservoirs, the syringe is held upright and several cubic centimeters of the lubricating fluid (saline or glucose) are drawn past the ring of reservoirs. The excess of the lubricating fluid is then expelled from the syringe, leaving two rows of reservoirs to lubricate the plunger of the syringe as it is worked back and forth.

The advantages of the self-lubricating syringe are:

1. A lack of need for changing of syringes due to freezing of the plunger in the barrel of the syringe.

2. There is less effort on the part of the operator in using the syringe due to ease of operation.

3. There is less likelihood of the needle slipping out of the vein due to lack of need for changing syringes in the giving of intravenous fluids as transfusions.

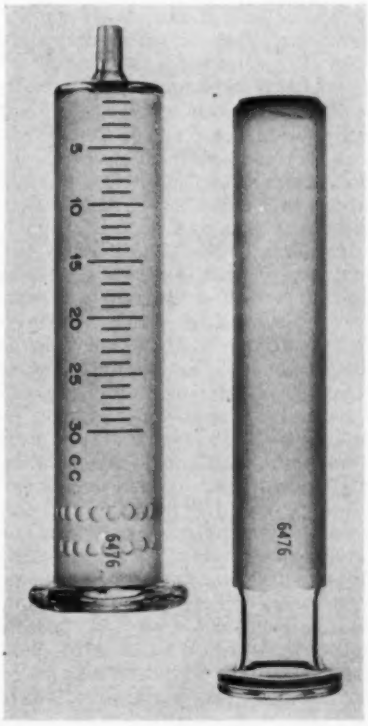

Fig. 1.

4. Lubrication may be through the same fluid as being given in the

From the Departments of Pediatrics of the St. Joseph's Children's Hospital and Baylor College of Medicine.

syringe or through a foreign fluid as saline in the giving of transfusions.

5. Ease of cleaning.

6. There is maintained a constant operating pressure through a wetting action on the barrel and plunger of the lubricating fluid.

COMMENT

The resident staffs have found a reservoir type of syringe of great value in the giving of intravenous fluids. Models have been made in 20 c.c. and 30 c.c. sizes. Anesthetists have found the reservoir for a self-lubricating type of syringe of value in the giving of intravenous anesthetics.

SUMMARY

A self-lubricating type of syringe from reservoirs in the barrel containing fluids for lubrication has been found to be of value in anesthetic and pediatric practice.

Case Reports

CELIAC DISEASE TREATED WITH POLYOXYETHYLENE SORBITAN MONOOLEATE*

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IN THE July, 1948, *Annals of Internal Medicine*, Chester Jones and his associates published an article entitled "Modification of Fat Absorption in the Digestive Tract by the Use of an Emulsifying Agent."[1] They used polyoxyethylene sorbitan monooleate known at that time as "Tween 80" and now referred to as PSM. PSM was fed to animals and human beings in large doses and for prolonged periods without any untoward symptoms or evidence of toxicity. Although they did not have a patient with celiac disease to which they might give PSM, they stated that in conditions of serious malnutrition due to poor fat absorption inherent in disturbances like celiac disease, the utilization of such a therapeutic measure might be beneficial. We have used the term celiac disease as defined by Nelson[2] as a chronic disturbance of nutrition of unknown cause in infants and children exhibiting poor absorption of fat and carbohydrate from the intestine as a primary defect.

The purpose of this report is, first, to give the history and findings of a 2-year-old girl suffering from severe celiac disease; second, to outline our investigation in establishing her diagnosis and its severity; third, to show her response when PSM was given to her while she was on a normal diet; fourth, to describe her present condition; and fifth, to suggest that PSM is an aid in the treatment of celiac disease.

CASE HISTORY

When H. J. was 6 months old, she was admitted to the pediatric service of Manchester Memorial Hospital suffering from pneumonia and diarrhea. Her early infancy had been uneventful. In the hospital her condition was such that she required oxygen, antibiotics, and transfusions. At this time it was noted that she had a large abdomen and that she passed large, loose stools. Stool examination showed no starch but much excess fat when she was on a diet containing cereal and whole milk. An x-ray of her abdomen showed pooling of the barium. X-rays of the long bones indicated general demineralization and rickets. She was discharged to her home on May 17, 1947, where she remained until she was admitted to Grace-New Haven Community Hospital in March, 1948, at the age of 18 months. On admission there was evidence of loss of weight, swollen abdomen, and copious, foul-smelling stools. At this time 49.5 per cent of ingested fat was recovered in the stools. Duodenal fluid showed normal trypsin activity. Intestinal x-rays showed a small-bowel pattern compatible with celiac disease. She was placed on a standard celiac diet with added vitamins A and D. Liver extract was given intramuscularly twice a week. She remained in the hospital for three months. The discharge diag-

*This chemical is marketed by Abbott Laboratories under the trade name of "Sorlate." International Vitamin Corporation calls it "Monitan." Both companies kindly furnished the material for use in this case.

nosis was "celiac disease which had improved under celiac diet."

After being home for three months, where the diet was not followed, H. J. entered Manchester Memorial Hospital again. She presented a picture very similar to that described on her entrance to the Grace-New Haven Community Hospital. The stools were copious, extremely foul-smelling, light in color, and mushy in consistency. She had no apparent subcutaneous fat except on her face. Her distended abdomen measured 56 cm. Although she was 2 years old, she was able to sit alone for only a few minutes; she did not creep; she did not talk or feed herself.

given by Anderson[3] for this age. Chart 1 shows the normal and celiac curves for vitamin A absorption when given in an oily medium, taken from the report of Breese and McCoord.[4] Chart 2 shows H. J.'s serum vitamin A when she was given 200,000 units of vitamin A as percomorphum oil and determinations made on blood drawn at three, five, and seven hours thereafter. It is practically a flat curve.

THE RESPONSE WITH PSM

PSM is a detergent which diminishes the size of fat globules by lowering their surface tension. Frazer[5] has stated that fat particles of small size

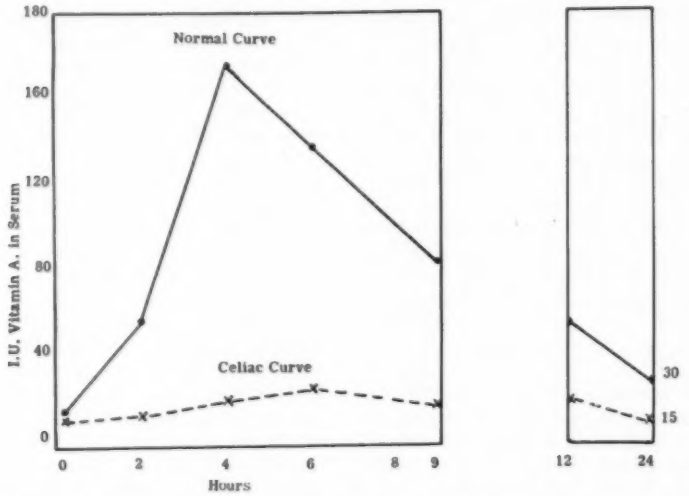

Chart 1.—Vitamin A absorption curve. (From Breese and McCoord: J. PEDIAT. 15: 183, 1939.)

INVESTIGATION

Investigation showed that H. J. had normal trypsin activity in her duodenal fluid. X-rays indicated osteoporosis of the long bones. She was placed on a diet of 120 Gm. carbohydrate, 45 Gm. protein, and 60 Gm. fat. Her average daily loss of fat, as determined from a three-day collection, was 30 Gm. This is considerably more than the normal of 0.35 to 1.79 as can be absorbed directly into the lacteals. In the October, 1950, issue of *Pediatrics,* Morales and collaborators[6] reported their investigation of the influence of particle size on the absorption of fat and vitamin A preparation in premature infants. They concluded that by reducing the particle size to 1 to 2 microns by homogenizing apparatus the absorption was greatly enhanced.

Chart 2 of our investigation of H. J. shows that when 0.99 Gm. of PSM was added to the 200,000 units of vitamin A, there was a slight elevation of the serum vitamin A. When 2.54 Gm. of PSM were added, there was considerable elevation in the serum vitamin A and an earlier appearance of the maximal value. Kramer and co-workers[7] obtained similar results by using the same material. Complete curves required so much blood that we were loath to take the required amounts. Since Pratt[8] had shown that a blood specimen taken five hours after ingestion gave an adequate indication of vitamin A absorption, we thereafter made only one determination five hours after the oral administration of vitamin A and PSM. Chart 3 shows the results on specimens taken five hours after the giving of 200,000 units of vitamin A with increasing amounts of PSM.

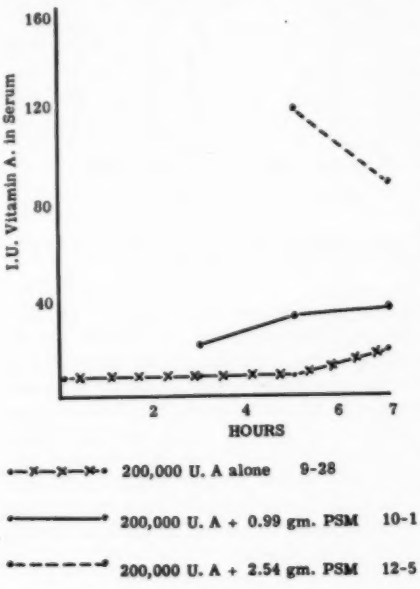

Chart 2.—Vitamin A absorption curves with and without PSM.

After this initial period of investigation the child was placed on a diet which contained about 145 Gm. of carbohydrate, 45 Gm. of protein, and 60 Gm. of fat to which was added increasing amounts of PSM. It was found by trial and error that 40 mg. of PSM were required for each gram of ingested fat to keep the daily fat content of the stools at 2 Gm. or less. The total daily quantity of PSM was divided equally between the three meals and was given at mealtime. On this quantity of PSM the stools appeared normal, they lost their previous foul odor, the abdomen became smaller, and the weight increased steadily. On several occasions we withdrew the PSM. Within twenty-four to forty-eight hours the stools had resumed their original character and the abdomen increased in size. Remissions and exacerbations of the disease could thus be produced at will.

When this child was discharged from the Manchester Memorial Hospital on Jan. 4, 1950, at the age of 3 years, 3 months, she was the picture of health. She had learned to creep, walk, talk, and adjust herself as one of the hospital family. Her psychiatric examination indicated an intelligence quotient of 95. She was 104 cm. tall and weighed 19 kilos. Her blood was normal. She is now in the process of being adopted. In September, 1950, she returned to the hospital to have a chylomicron count done, as outlined by Elghammer and associates.[9] This showed that she had a normal fat absorption. H. J. has, therefore, received no PSM since that time. She is now perfectly well and without any symptoms of celiac disease.

Those of us who were observing this child were much impressed by how much happier she was on a full diet with added PSM than when she was on a restricted diet as is generally given to children with celiac disease. We feel that this girl's general condition was so much improved

that she was not suubject to the hazards which accompany the usual course of the disease while waiting for spontaneous remission. Our experience indicated that PSM should prove useful in the treatment of celiac disease.

SUMMARY

A child is reported who had typical and severe celiac disease. This was treated with unusual success by the simple addition to her meals of PSM in the ratio of 40 mg. of PSM to each gram of ingested fat. The use of this emulsifying material permitted her to eat a normal full diet and to live in a state of complete remission until spontaneous recovery from the disease took place. A second child has also been enabled to enjoy complete clinical remission while taking PSM, although she still depends upon its regular use. We suggest PSM as an aid in treating celiac disease.

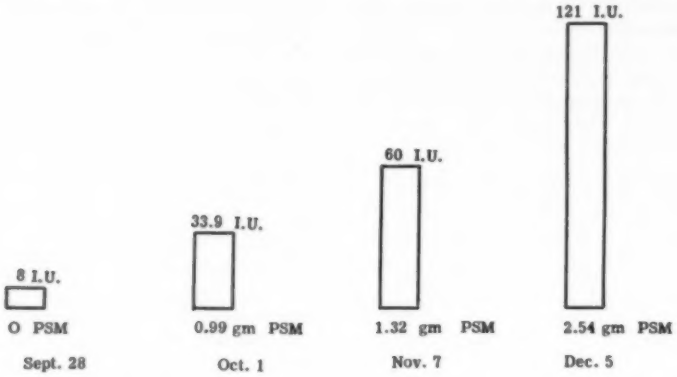

Chart 3.—Serum values of vitamin A as International Units five hours after varying amounts of PSM were added to 200,000 I.U. of vitamin A by mouth.

Although H. J. was the only case of celiac disease whom we kept under such close and prolonged observation, one of us (H. B.) had a child with celiac disease which he had followed for seven years. She had distressing relapses and stunting of growth in spite of eating a strict diet. On Feb. 21, 1949, at the age of 6 years, she was placed on a full diet with the addition of PSM in the ratio of 40 mg. of PSM for each gram of fat ingested. At that time she was 106.7 cm. tall, which was the expected height of a 4-year-old as given by Nelson.[10] She was 7.6 cm. shorter than her 5-year-old sister. Since instituting PSM she has had no relapses. After sixteen months she had grown 8.25 cm. in height, her normal rate.[10] She is now a happy, healthy, growing child. A chylomicron count done in September, 1950, showed that she had about one-half the normal fat absorption when no PSM was added to her meals, whereas with PSM the chylomicron count was just slightly below normal.

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ACUTE THROMBOSIS OF THE FEMORAL ARTERY IN AN INFANT

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PUNCTURE of the femoral vein to obtain analytical blood samples is a routine procedure widely used in pediatric practice. The method generally does not entail great difficulty or danger, but injury to the vascular channels is a possibility which may be encountered. We wish to present the following case to illustrate a manifestation of this complication and to review the treatment of such vascular accidents.

CASE REPORT

L. E., a 1-year-old white male child, was admitted to the pediatric ward of the Beth-El Hospital on Oct. 23, 1948, with a history and clinical picture of classical lipoid nephrosis. Except for a diarrhea with severe dehydration for which the infant was hospitalized at the age of 5 days, the patient had been well until ten days before this admission when edema of both eyelids appeared. The swelling was considered a local condition and the child was given penicillin intramuscularly and an antihistaminic by mouth. Persistence of the edema of the lids, onset of swelling of the legs and abdomen, and a urinary frequency of twenty times per twenty-four-hour interval led the family to seek further medical attention. The child was then admitted to the Beth-El Hospital.

Admission examination revealed a well-built 1-year-old child with generalized edema. There was a moderate inflammation of the tonsils and the eardrums. Heart and lungs were normal. Blood pressure was 126/74. A small abdominal fluid wave could be elicited. Urine specimens showed a trace of albumin, and scattered white blood cells were seen in the sediment. A blood sample was obtained by femoral vein puncture and showed a urea nitrogen of 12.5 mg., cholesterol of 460 mg. per cent, cholesterol ester of 200 mg. per cent, sugar of 80 mg. per cent, and a total protein of 5.4 Gm. Blood culture was negative. The patient's condition remained stationary until October 26, when the femoral vein tap was repeated. The blood chemistry determinations were almost identical with the previous study but total protein was 5.6 Gm. with an albumin of 2.6 and a globulin of 3.0 Gm. This picture of edema, ascites, albuminuria, hypercholesterolemia and total protein diminution with reversal of A/G ratio confirmed the clinical diagnosis of lipoid nephrosis.

On October 27, twenty-four hours after the second femoral vein puncture, small cyanotic areas were noted on the right foot. Within the next forty-eight hours the entire right lower extremity became cyanotic, cold, and mottled, and the patient began to scream out occasionally as though in pain.

On October 29, the child was seen by one of us (S. F.), when the entire right limb was found to be cold, pale, and cyanotic. Palpation revealed all pulsations on the right leg to be absent up to the femoral where the pulse was markedly diminished. Oscillometric readings were zero at the ankle, and below and above the knee. On the left, pulses were present at all levels and oscillometric readings were normal. A diagnosis of femoral artery thrombosis

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with marked secondary vasospasm was made and the patient was placed on the following therapeutic regime:

1. Sedation—Demerol, 10 mg. q. 4 h.
2. Anticoagulants—Depo-Heparin,* 50 mg. intramuscularly, q. 6 h. Dicumarol, 50 mg. as an initial dose by mouth.
3. Wrapping of involved limb in sterile gauze and then absorbent cotton.
4. Antibiotics—Penicillin, 300,000 U. intramuscularly daily.
5. Repeated lumbar paravertebral ganglion blocks of L_1 to L_4 with 3 to 5 c.c. of 1 per cent procaine at each ganglion site. These were given for five consecutive days and then every other day for ten days.
6. Elevation of the head of the bed on six-inch blocks.

This picture, where prognosis for the involved limb appeared grave, began to show improvement within the first seventy-two hours of active treatment. The affected leg became warmer although cyanosis persisted. Trophic changes were limited to the right foot and lower one-quarter of the leg where the skin became shiny and dry. On December 5, Dicumarol was discontinued because of the precipitous effect of minimal doses of this drug on the prothrombin time. Anticoagulant effect was maintained by administration of Depo-Heparin intramuscularly in doses of 50 mg. q. 6 h.

One week after onset of the occlusive symptoms (December 6), the right leg was warm; cyanosis and mottling were almost completely gone. Palpation revealed that none of the pulsations had returned although the femoral artery impulse was decidedly stronger. Oscillometry was unchanged.

Except for the appearance of an acute diarrhea which readily responded to dietary and parenteral measures, the subsequent hospital course was uneventful. For several days during the course of the diarrhea the child was on continuous intravenous infusion which permitted administration of the heparin in its aqueous form by direct addition to the intravenous. The dose was 100 mg. for each twenty-four-hour period.

On December 21, anticoagulant therapy was discontinued, and the child was discharged two days later. At this time both legs were warm but the skin in the region of the right lower leg and foot, which had become shiny and dry, now showed a scattered focal slough and desquamation of the superficial layers. The nephrotic syndrome had cleared entirely except for persistence of the albuminuria.

*Depo-Heparin was made available through the courtesy of The Upjohn Company.

DISCUSSION

The subject of arterial embolism and thrombosis in infancy has been thoroughly reviewed by Gross[1] in 1945. His paper concerns itself with a review of forty-one cases collected from the literature, as well as a detailed discussion of six cases which he personally observed. Of greatest interest to this presentation is the analysis of etiological factors.

1. Sepsis: In general, infection must be overwhelming to cause thrombotic processes. These thromboses may be evident as circumscribed necrotic foci following pyemic dissemination or may result from the fragmentation into the general circulation of septic cardiac vegetations with secondary major embolism. In either case, the clinical picture is characterized by a marked toxicity of the patient.

2. Trauma: Various forms of pressure and injury arising as part of the birth mechanism may cause thrombosis. One example would be gangrene of an arm due to an encircling, constricting umbilical cord.

3. Atypical closure of the ductus arteriosus: Cases of thrombosis within the duct and protrusion of the clot at either end have been described. Fragmentation of a portion of the thrombus could result in either pulmonary or peripheral embolism. Gross describes two such cases, one in a 13-month-old

child. Rarer occurrences of this entity in adults have been reported.[2, 3]

4. Umbilical arterial thrombosis: The thrombotic process which closes the umbilical arteries may rarely extend into the hypogastric, iliac, and even into the lower end of the aorta. This may conceivably interfere with the blood flow to the lower extremities.

Recently, a neonatal syndrome of vascular disturbances has been described by Mills[4] in newborn infants. All patients observed required resuscitation and injection of nikethamide into the umbilical cord. The hypothesis presented, postulates accidental injection of the drug into the umbilical artery instead of into the vein with retrograde flow into the hypogastric artery, the actual pathology being due to prolonged arterial spasm with secondary thrombosis.

Reviewing the present case in the light of the foregoing discussion of etiology, the most likely pathologic process appears to be a traumatic one, with the following course:

1. (a) Injury to the wall of the artery producing either mural hemorrhage and then intraluminal thrombosis, or (b) precipitation of an intense vasospasm with secondary thrombosis.

2. After the occlusive mechanism was established, distal and proximal propagation of the thrombus completing the shutdown of arterial blood flow.

The appearance of a damaged blood supply in an infant requires prompt institution of therapeutic measures. It is important to inspect the involved extremity frequently for the first appearance of gross trophic changes as well as to follow carefully the general condition of the patient. The presence and spread of infection and the onset of toxic symptoms may require radical surgical intervention. It is a general impression, however, that prognosis for limb and life in cases of acute arterial insufficiency is in proportion to the patient's age. This impression is even more prominent when dealing with infants where the process of collateralization seems to exhibit the greatest adaptability.[1] A general medical regime should include the following essentials:

1. Sedation: While it is not axiomatic that sudden arterial occlusions are accompanied by pain, the greater number of such cases do involve pain of great intensity. Prompt and adequate control of this complaint is important since the emotional factor enters into the increase of the vasospastic element. It appears better to utilize drugs which do not potentiate vasoconstrictor tone. Demerol is valuable for this reason. Papaverine is ideal although relief of pain by this drug is not as dramatic as its vasodilatory effect.

2. Paravertebral sympathetic nerve blocks: Performance of these blocks is a routine in our treatment of acute vascular catastrophes. The interruption of the reflex arc set up at the injured vascular segment relieves the vasospasm at the site of injury, allows maintenance of the collateral vascular bed, and in many instances relieves the pain.

3. Protection of limb from infection and trauma: The extremity should be wrapped in sterile gauze and then in several layers of absorbent cotton.

4. Change in position of the patient: The head of the bed should be elevated on blocks to augment the head of arterial blood pressure (with the force of gravity), toward the periphery.

5. Anticoagulants: Undoubtedly the most widely used plan of administration of anticoagulants employs heparin for immediate effect and, at the same time, commences administration of Dicumarol by mouth. The heparin is discontinued when therapeutic effect of Dicumarol is attained as reflected in the prothrombin time determinations.

In the present case, Dicumarol was discontinued and the anticoagulant effect was maintained with the intramuscular form of heparin. When one considers the clinical result obtained and compares heparin and Dicumarol

as to toxicity, duration of action, and ease of neutralization, it seems to warrant further study along the lines of utilizing heparin alone in anticoagulant treatment.

6. An important prohibition should be included in all discussions of treatment of arterial insufficiency. Under no circumstances should heat in any form be applied to the acutely ischemic limb. Since the pathology is one of diminished blood supply, it is physiologically incorrect to apply an agent which increases cellular metabolism and oxygen consumption. Placing such an extra and insurmountable burden on an already deficient circulation too often accelerates the appearance of ulceration and gangrene.

SUMMARY

A case of thrombosis of the femoral artery following a femoral vein puncture procedure has been presented. Etiology of gangrene of the extremities in infants has been reviewed and a regime of medical therapy outlined.

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TWIN FETUSES IN FETU

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RETROPERITONEAL teratomatous tumors are unusual and those possessing well-formed organs and fetal membranes are distinctly rare. However infrequent, these lesions are of particular interest to pediatricians since approximately one-half of all retroperitoneal teratomas manifest themselves in early life.[1] Recently, at The Children's Hospital of Boston, we have had the opportunity to care for a newborn infant with a most unusual type of retroperitoneal teratoma, one in which these were twin fetuses in fetu. To our knowledge, such a case has not been reported previously.

A fetus in fetu does not arise from fertilization of an ovum within a child. Instead, it represents a splitting off of cells from a developing embryo, the growth of which produces a teratoma, encased within the host child. Unattached retroperitoneal teratomas may achieve any degree of differentiation. In simplest form they are mere dermoid cysts or rudimentary teratoid tumors, but in more complex specimens a teratoma can exhibit easily recognizable fetal membranes, somites, organs, and appendages. A fetus in fetu is a highly developed or complex form of teratoma.

Meeray and Frazier,[13] Arnheim,[3] and O'Leary and Halpert[15] have reviewed all types of retroperitoneal teratomas. Together they have collected a group which include twenty-nine in patients under 18 years of age. Gould and Pyle[8] collected eleven cases of "fetus in fetu" of which six occurred in children. Von Haberer,[11] Brunkow,[4] and Farris[7] have each added one case which with our own makes a total of ten. In the whole group of thirty-nine pathologically similar lesions, twenty-five were found in subjects less than 2 years of age. The sex incidence was equally divided, which might suggest a different genesis from sacrococcygeal tumors in which females outnumber males by four to one.[9]

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CASE REPORT

M. O., A315002, a white female infant, was referred to the Hospital by Dr. Paul A. DesHopagian, Chelsea, Mass., and admitted on Feb. 9, 1947, at the age of 2 days.

The family history was of interest. Of five previous pregnancies, three ended with early miscarriages and the fourth produced an infant who succumbed at 4 years of age to a congenital form of internal hydrocephalus. From the fifth there was a normal boy, who was currently 3 years old. There was no history of other congenital anomaly or of twin births.

The pregnancy had been normal, running to full term; no viral or other infections occurred during pregnancy. The labor was spontaneous, and the delivery normal. Birth weight was 7 pounds, 2 ounces.

The present illness began on the second day of life when the infant regurgitated all feedings and some bile-stained mucus. Several meconium stools were passed. The abdomen was found to be distended and a mass was palpable in the epigastrium.

On physical examination the infant was slightly dehydrated, mildly icteric, and obviously distended. A movable, lobulated, partially cystic mass approximately 8 cm. x 5 cm. x 5 cm. in dimensions occupied the upper portion of the abdomen and extended well out toward the flanks particularly toward the right. The mass could be sepa-

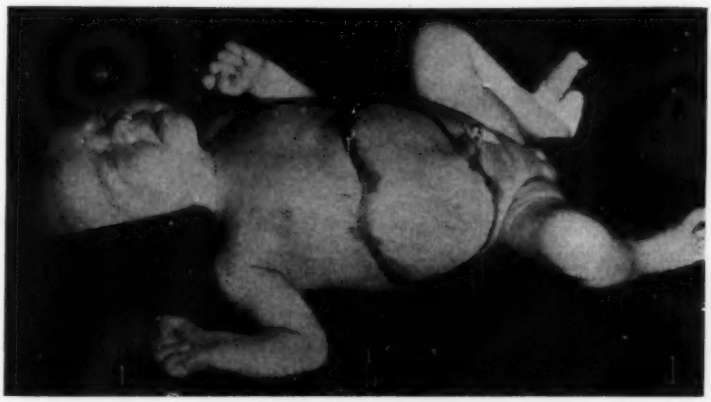

Fig. 1.—Photograph of newborn baby. The intra-abdominal mass is outlined in crayon.

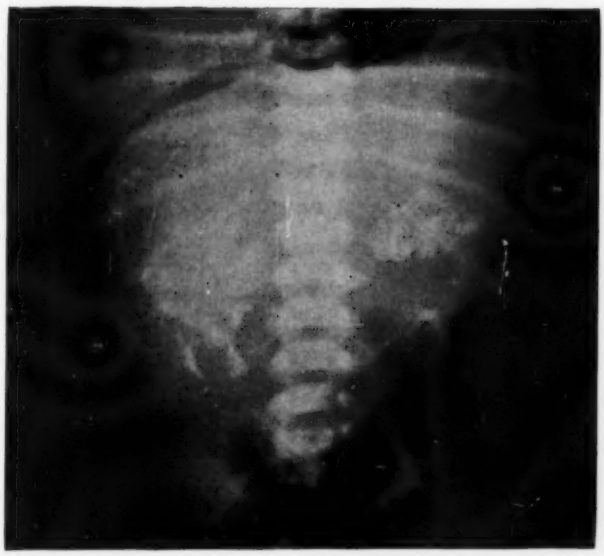

Fig. 2.—Roentgenogram of baby, showing the intra-abdominal calcified structures.

rated from the liver edge. It was barely palpable on rectal examination.

The usual routine laboratory studies were not remarkable. The plasma nonprotein nitrogen was 57 mg. per cent prior to administration of intravenous fluids.

Roentgenographic studies including intravenous excretory urograms were carried out during the day of admission and were interpreted by Dr. Edward B. D. Neuhauser as follows: "There is a large soft tissue mass within the abdomen which deforms the stomach, displaces the duodenum upward and to the right, and the remaining bowel downward and to the left. Within this very large soft tissue mass there is a moderate amount of amorphous bone and an almost complete fetal skeleton of which the skull, spine, and some of the long bones can be identified. Intravenous pyelogram shows displacement of the dye-filled left kidney laterally, downward, and posteriorly. The right kidney cannot be identified. The previously described mass produces an extrinsic pressure defect in the dome of the bladder."

In the hospital, oral feedings were poorly tolerated. No "fetal" movements were seen in the parasitic mass. Electrocardiographic studies with special abdominal leads elicited no abnormalities.

With a preoperative diagnosis of fetus in fetu, the infant was operated upon Feb. 12, 1947, under ether anesthesia. The abdomen was opened through a long right rectus muscle-retracting incision. A fist-sized mass was found lying behind the gastrocolic ligament and in front of the pancreas. The gastrocolic omentum was opened and the mass, completely enclosed in a sac, could be readily dissected free from the displaced stomach, pylorus, and duodenum. The entire structure obtained its blood supply from the base of the mesentery, where there were vessels which communicated with the superior mesenteric artery and vein; the nutrient vessels were individually ligated and divided. The mass appeared to be cleanly excised, and there was no visible or palpable placenta-like structure or sac remaining in the child's abdomen. The gastrocolic omentum was repaired and the abdomen was closed in a routine fashion.

Postoperatively, the infant developed a mild diarrhea on the sixth postoperative day which responded well to parenteral therapy and she was discharged home on the tenth postoperative day. During the three and one-half years since operation there has been no evidence of recurrence of the tumor and the child's general development has been gratifyingly normal.

The surgical specimen was examined by Dr. Sidney Farber of the Department of Pathology, and by Dr. J. Lewis Bremer, consulting embryologist to The Children's Hospital.

Gross Description.—Weight was 289 grams. The mass was encased in a grayish and opaque capsule, about 0.5 mm. in thickness; this was smooth over its entire surface except at the site where it was severed at operation from the mesentery of its host. About 50 c.c. of slightly cloudy yellow fluid could be aspirated from the sac, which on analysis showed the following: total protein 51.3 mg. per cent, pH 8.1, chloride 119 meq. per liter, bilirubin (free) 0.5, total bilirubin 1.7.

The membranous covering was incised and two unequal sacs were found which were fused in the middle, so that the entire structure was a bilocular formation. Within the larger sac was a rather well-formed fetus (estimated age, 4 months). There were two well-formed cephalad and caudad extremities with three phalangeal buds on the right hand extremity. Between the buttocks was a discrete elevation, the genital papilla. The anus was imperforate. On the head were two well-developed eye spots and an ill-defined stoma. Within the smaller sac was a poorly formed embryonic mass with a cystic cephalic

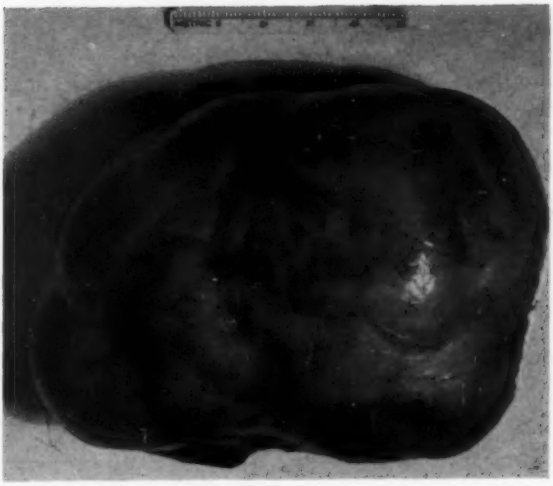

Fig. 3.—Specimen which was removed, showing sac before it was cut open.

Fig. 4.—Specimen, with sac cut open and displaced to the upper left. At lower left is the head and a limb bud of the less perfectly formed fetus. On the right is the well-formed fetus, with its flexed head and limb buds.

portion and with identifiable extremities attached to an amorphous-appearing trunk. Both fetuses possessed cordlike structures passing from the embryo to the thickened area on the sac wall from which the nutrient vessels emerged.

Microscopic Study.—Sections were taken from the fetal membranes, including the area where it was attached to the host and also from the genital ridge of both fetuses. The fetal membrane was composed of one layer of condensed fibrous tissue lined on the inner side with a thin sheet of squamous epithelium continuous with the skin of the embryo. Covering most of the outer surface of the sac there was peritoneum, but attached to its posterior surface there were a few fragments of pancreatic and areolar tissue.

The small area whereby the mass had been attached to the patient was carefully examined for placental tissue. It was composed of contiguous coils of alimentary tract epithelium derived from the yolk stalk. There was no trophoblastic or true placental tissue.

Several sections of the genital ridge of each embryo were negative for cells resembling primordial germ cells or nephrogenic tissue. All mitotic figures that could be found contained what appeared to be a normal complement of chromosomes.

PATHOGENESIS

The pathogenesis of teratomatous growths of the nature of "fetus in fetu" have not only concerned medical writers since earliest times, but it still remains a most controversial subject. Though the literature abounds with morphological descriptions, few facts regarding pathogenesis have been forthcoming. As a plausible explanation for the development of a fetus in fetu, we present briefly two plausible theories:

1. Incomplete monozygomatous twinning has occurred at an early age when the budding or isolated cell mass is totipotential or nearly so; this side mass has continued to develop and has been included in the maturing sister embryo. In support of the theory of incomplete monozygomatous twinning one finds considerable indirect evidence. Twinning, complete or incomplete, is a frequent response of a developing embryo to hereditary stimulus or to adverse circumstances. Danforth[5] has succeeded in breeding a strain of mice which produce incomplete external duplication of the hind legs in 20 per cent of the live offspring. Arey[1] has demonstrated that ectopic tubal implantation increases the incidence of twinning, whether it is complete or incomplete. Many physical or chemical agents have been shown in experimental studies to produce twinning to various degrees of completeness.[10] Obviously, the reproduction potential as evidenced by twinning in one individual embryo may be more highly developed than in another. It is not unlikely that minor environmental aberrations would, if present at a critical period, stimulate abnormal division in a developing cell mass. The actual mechanisms of incomplete and included twinning have been described in detail in standard texts.[2, 16]

2. A sex or germ cell in the retroperitoneal region (where they are normally found) has been parthenogenically stimulated and has developed into a twin rudimentary fetus. Loeb[12] has observed embryonic and placental ectoderm in infertile immature guinea pig ovaries. Pincus[17] has demonstrated that parthenogenic fertilization in mammals was feasible when he obtained live young rabbits from pathogenically stimulated eggs which were reimplanted into sensitized rabbit uteri.

SIGNS AND SYMPTOMS

As a group, retroperitoneal teratomas exhibit a paucity of signs. Vague gastrointestinal distress and enlarging abdomen are the outstanding

findings. Genitourinary tract involvement is not common. Lumbar back pain or abdominal discomfort may be present in older children. The physical signs are often sufficient to lead the examiner to suspect the correct diagnosis and carry out further study. An irregular abdominal mass which varies in consistency is commonly observed. It may be in the epigastrium but is more likely to protrude from either paravertebral gutter.

Roentgenologic examination discloses amorphous calcification in about half of all teratomas but it is well to remember that calcareous deposits are also frequently seen in degenerating tumors of other types. Whenever film studies show well-developed skeletal structures, the diagnosis of fetus in fetu can be made with great certainty.

Differential diagnoses should include consideration of the more commonly seen retroperitoneal masses such as hydronephrosis, polycystic kidney, embryoma of the kidney (Wilms' tumor), and neuroblastoma sympathicum. Intra-abdominal enteric cysts (duplications), mesenteric or omental (lymphangiomatous) cysts may be confused with a movable retroperitoneal lesion. Intravenous pyelography is recommended in all cases of intra-abdominal mass in infancy and childhood. It is an important aid in the differential diagnosis and it can tell the surgeon whether there are bilaterally functioning kidneys prior to surgical intervention.

TREATMENT

Of the "fetus in fetu" group with which we are primarily concerned here, there have been four previous instances of a successful surgical removal. McNutt in 1894[14] removed a five-pound "fetus" within a ten-pound cyst from the right flank of an 11-year-old boy whose recovery was "rapid and complete." von Haberer[11] excised a five-pound encysted fetus from the retroperitoneal space of a 4-year-old girl. The wound healed per primam. Brunkow[4] and Farris[7] have each reported a case in which the encysted fetus has been delivered and the membranes marsupialized, in preference to excision of the entire lesion. In Brunkow's case there was drainage for six weeks postoperatively, following which the opening sealed over and the patient was presumably well. Farris noted that the fluid reaccumulated in the remaining cyst postoperatively but was then apparently spontaneously resorbed.

There has recently been a tendency to disregard the complete removal of a fetus in fetu and its membranes, in favor of the easier operation of incising the fetal membrane, extracting the fetal monster, and then marsupializing the remaining sac. This latter type of procedure has been quite acceptable when handling a pregnant woman who has an ectopic intra-abdominal pregnancy. Here, the fortuitous disappearance of the remaining fetal membranes by autolysis and sloughing can be expected. However, it should be emphasized that in ectopic pregnancy one is dealing with the membranes of a heterozygomatous offspring, capable of independent existence, while in instances of fetus in fetu one is dealing with a monozygomatous included twin parasite which has developed parallel with, has been totally dependent upon its host, and presumably is composed of tissues which are potentially neoplastic. To leave membranes or any other portion of a fetus in fetu in the host invites the possibility of developing local recurrence or even metastatic spread. Hence there can be little doubt about the advisability of removing *all* abnormal tissues when operating upon a fetus in fetu, for only in this way can there be a reasonable chance of avoiding a subsequent malignant degeneration.

Radiation therapy has no place in the initial treatment of operable teratomatous lesions. Any subsequent recurrences or metastases may temporarily respond to palliative or intensive x-ray therapy, but no cures in

children by this method have been reported.

SUMMARY

Description is given of twin "fetuses in fetu" which were successfully removed from a female infant on the fifth day of life. A brief summary of the literature is presented, including pathogenesis, descriptions, and treatments of these lesions.

A fetus in fetu is a form of teratoma, and it should always be removed, along with its membranes, to insure a cure.

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STOMATITIS AND DIARRHEA IN INFANTS CAUSED BY BACILLUS MUCOSUS CAPSULATUS

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IN JANUARY, 1946, Walcher[1] published a paper in which the organism *Bacillus mucosus capsulatus* was reported as the probable etiological agent in an epidemic of diarrhea involving infants from 6 weeks to 10 months of age. More recently,[2] he employed serologic methods in order to classify the organisms recovered in this epidemic more adequately.

In April, 1948, Faucett and Miller[3] reported *B. mucosus capsulatus* as a cause of a stomatitis which bore some resemblance to thrush, but could be differentiated from thrush by a greater tendency to confluency and a heavier, dirtier-appearing membrane. This stomatitis did not respond to the usual forms of local treatment used in thrush, but a dramatic recovery resulted when sulfadiazine was given orally.

Since the publication of the above articles there have been no secondary reports of *B. mucosus capsulatus* as a cause of infantile diarrhea or stomatitis, nor have we been able to find reference to any case in which this organism has been the causative agent of both diarrhea and stomatitis in the same patient. Therefore, we deemed it worth while to report the cases of premature twins, both of whom developed diarrhea and one of whom, in addition, developed a stomatitis, in which a gram-negative capsule-bearing bacillus, considered to belong to the Friedländer group, was recovered.

CASE REPORT

On Oct. 1, 1949, premature female twins of thirty-six weeks' gestation, weighing 1,680 grams (Twin A) and 1,920 grams (Twin B), respectively, were born of a young Spanish primipara at the Beth-El hospital. There was one placenta. The twins were in good condition at birth and there were no abnormal physical findings. They were immediately placed in the premature nursery where they were given the routine premature care employed at this institution.[4] On the eleventh day of life, both twins, who had been progressing well, simultaneously developed loose, watery, green stools. In addition it was noted that Twin A had a stomatitis which was characterized by a dirty, white, firmly adherent membrane on the left buccal mucosa, hard palate, and tongue. The twins were immediately isolated, cultures of the mouth and stools were taken, and a diarrhea therapy regime, consisting of a period of starvation, parenteral fluids, and the gradual reinstitution of oral feedings with protein milk, was started. Cultures of the stools of both twins and of the mouth of Twin A grew out luxurious colonies of a gram-negative capsule-bearing bacillus belonging to the *B. mucosus capsulatus* group. The diarrhea in both infants was improving but the stomatitis in twin A was still present when the culture reports were obtained. Sulfadiazine, 0.06 Gm. per pound of body weight per twenty-four hours, was given by mouth in divided doses at four-hour intervals. Forty-eight hours later the stools were normal and the stomatitis of Twin A was cleared of membrane but her mouth remained inflamed. Cultures at this time still revealed luxurious colonies of gram-negative capsule-bearing bacilli in the stools of both and in the mouth of only Twin A. Be-

From the Department of Pediatrics Dr. Harry R. Litchfield, Chairman, Beth-El Hospital.

cause of the persistence of positive cultures and of their possible epidemiologic significance, sulfadiazine therapy was discontinued and aureomycin, 25 mg. per pound of body weight per twenty-four hours, was given orally in divided doses at six-hour intervals. On this therapy the organism disappeared from the mouth of Twin A in twenty-four hours, but four days of treatment were required before the stools began to show a decrease in organisms. It took a total of seven days to eradicate the organism from the stools. The twins were discharged on the thirty-seventh day of life in good condition, weighing 2,460 grams and 2,640 grams, respectively.

COMMENT

The case of Twin A, we believe, is the first in which both stomatitis and diarrhea caused by *B. mucosus capsulatus* is reported. Walcher[1] makes no mention of stomatitis in his reported outbreak of diarrhea and Faucett and Miller[3] specifically state that diarrhea occurred in none of their six infants with stomatitis.

Although sulfadiazine improved the clinical condition in our patients, it did not eradicate the organisms, and thus a source of possible reinfection or carrier state existed. Since aureomycin had been shown to be effective in infections caused by *Klebsiella pneumoniae* (*B. mucosus capsulatus*, Friedländer's bacillus),[5] it was employed in our cases with gratifying results.

SUMMARY

B. mucosus capsulatus is reported as the causative agent of diarrhea occurring in two premature twins. One twin, in addition, had a membranous stomatitis due to the same organism. Sulfadiazine therapy improved the clinical condition, but aureomycin was necessary to eradicate the organism.

We wish to thank Miss G. Rabinowitz of the Department of Laboratories of the Beth-El Hospital for her assistance with this work.

ADDENDUM

Subcultures of the organism recovered from these patients were submitted to Dr. Dwain Walcher for study. He discovered this organism to be serologically identical with that which he recovered and identified on the etiological agent in an outbreak in diarrhea in infants.[1, 2] Dr. Walcher's results with our organism is as follows: "... to my great interest I found that the colonial appearance was very comparable to that of the organism initially described. After repeated subculturing was done, the organisms were set up against some of the stock sera which had been prepared at the time the study was done. As you will note from the table below, these organisms appeared to be serologically identical with those described ..."[6]

	1:10	1:100	1:1,000	1:10,000
A. Stool	4+	4+	4+	3+
Throat	4+	4+	4+	4+
B. Stool	4+	4+	2+	1+
Throat	4+	4+	2+	0

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Clinical Conference

CONFERENCE AT RAYMOND BLANK MEMORIAL HOSPITAL FOR CHILDREN, DES MOINES, IOWA

LEE FORREST HILL, M.D., CHIEF OF PEDIATRIC STAFF

DR. HILL.—Our first case was presented at clinic two weeks ago. We are presenting it again this morning because in the interval an operation has been done and we can now give you a more complete story. Dr. Byrum, will you tell us about the baby?

Case 1. Congenital Cystic Disease of the Lung

DR. R. J. BYRUM (Resident).—This is an 8-week-old white male infant referred to this hospital by the family physician, Dr. Harold Peasley, because of a persistent paroxysmal cough which began when the baby was 1 week old. Birth was at full term, spontaneous, and without incident. Birth weight was 7½ pounds and at the time of admission had increased to 11 pounds on breast feedings. Five or six rather severe paroxysms of cough have occurred daily. The baby has not been feverish at any time, and no signs of a cold have been noted by the parents. Respirations have frequently been observed to be abnormally rapid, but dyspnea, to any marked degree, and cyanosis have been absent. Choking on feedings has not occurred at any time, nor has there been vomiting or diarrhea.

Physical examination at the time of admission showed an alert, well-nourished infant in no apparent distress. However, on percussion, hyperresonance was found over the entire left chest. The apical cardiac thrust was felt just to the left of the sternal margin, and dullness extended well to the right of the sternum. The trachea, by palpation in the suprasternal notch, was noted to deviate far to the right. Breath sounds were absent on the left, but appeared to be normal on the right. There were no other significant physical findings.

Red cells numbered 3,000,000 and the hemoglobin was 10 Gm. The white blood count was 10,150 with 69 per cent lymphocytes. Urinalysis was negative. Our initial clinical impression was pneumothorax on the left, but roentgenograms were not confirmatory. Perhaps Dr. McMillan will describe the films.

DR. J. T. MCMILLAN (Radiologist).—These are the posteroanterior and lateral chest films on this infant. You can see that the heart and mediastinum are displaced markedly to the right and that the area of the left lung is filled with a large air-containing cystic lesion. The cyst herniates into the mediastinum and also compresses what is probably normal lung tissue inferiorly. Lung markings can be seen extending out through the cystic area to the lateral thoracic wall, indicating that this is a cyst and not a pneumothorax. The right lung is apparently normal although it is largely obscured by the dextro-situated heart and mediastinum.

Under the fluoroscope the right hemidiaphragm was observed to move normally, but the left hemidiaphragm was quite limited in its excursion due

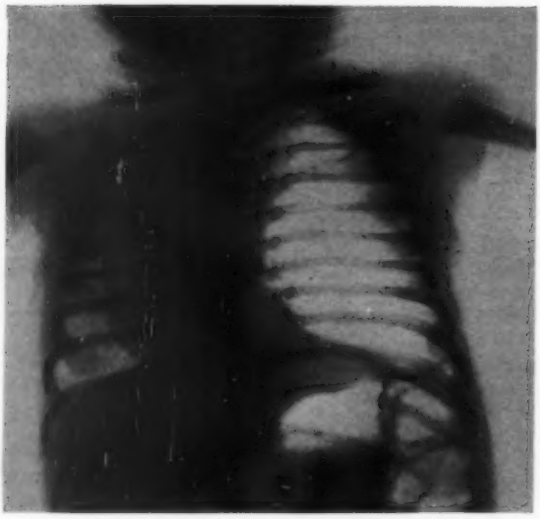

Fig. 1.—Anteroposterior roentgenogram showing cystic left lung, dextro-position of heart and mediastinum, fine trabeculations within cyst, and compressed lung above left diaphragm.

Fig. 2.—Roentgenogram two months following lobectomy shows restoration of heart and mediastinum to midline, and aeration of remaining left lung.

to the cystic lung. A swallow of barium revealed that the esophagus was displaced to the right, and also excluded the possibility of a diaphragmatic hernia.

It is our opinion that these findings represent a large congenital cyst, involving most of the left lung.

DR. HILL.—Those of you who were here two weeks ago will recall that we had a rather lively discussion about what should be done for this baby. The fact that he had been so little disturbed by such an extensive involvement as is seen in the x-ray films, raised the question of conservative watchful waiting. Against this it was argued that there was little if any functioning left lung, that the right lung was partially compressed by the dextro-position of the heart and mediastinum, and that the advent of a respiratory infection or other untoward complication might seriously jeopardize the baby's chances for survival. Simple aspiration of the air in the cyst could accomplish little but temporary relief, since the cyst would shortly refill, and besides there was the risk of introducing infection or of creating a pneumothorax. Marsupialization of the cyst was discussed by the chest surgeon Dr. Dorner. It was his recommendation, however, that the procedure of choice was surgical removal of the cyst. This was done and Dr. Dorner will tell us what he found.

DR. R. A. DORNER.—The left interspace was opened, exposing a normal-appearing parietal pleura. As this layer was divided there was no escape of air, thus excluding the possibility of pneumothorax. The cystic lung immediately presented. Inspection showed the cyst filling most of the chest cavity. Further inspection revealed a mass of completely atelectatic lung with the color and consistency of splenic tissue at the hilus. There was a small layer of normal-appearing lung tissue on the diaphragmatic surface of the cyst. The cyst was opened with the thought that it might be shelled out to save this lower portion of lung tissue. This proved impractical and the entire lower lobe containing the cyst was removed. With positive pressure through the intratracheal anesthesia apparatus, the previously atelectatic mass of lung tissue almost completely expanded. The baby stood the operation very well and was returned to his room in excellent condition. No postoperative complications have occurred. As you see in this postoperative film, the expanded left upper lobe nearly fills the left chest cavity, and the mediastinal structures have returned to their normal positions. In my opinion, it is most unlikely that spontaneous expansion of this lobe would have occurred so long as the cyst remained distended.

DR. HILL.—Dr. Birge, what did the pathological examination of the cyst show?

DR. R. F. BIRGE (Pathologist).—The specimen was a 31 gram portion of pulmonary tissue said to represent the lower lobe of the left lung. Occupying the upper two-thirds of the substance of the lobe was a 6 cm. oval cavity which had been previously opened. The lining surface of the cavity presented a distinctly trabeculated appearance, and one could see many various-sized small out-pouchings extending from the main cavity into the substance of the base of the lobe. The lining surfaces were smooth and pink

Fig. 3.—Photograph shows left lower lobe with unilocular cyst and trabeculations coursing through it. Compressed lower portion of lung is at top.

in hue. Except for moderate atelectasis, the surrounding pulmonary parenchyma was unremarkable. The bronchi seemed normal. No communication between the lumen of a bronchus and the cyst cavity could be established by the use of a tiny probe.

The cavity was found, on microscopic study, to be covered by bronchial mucosa including muscularis mucosa. It presented numerous small evaginations, all lined by bronchial mucosa, and occasionally included portions of hyaline cartilage.

In the absence of infection, one must consider this lesion to represent a congenital malformation of the lung. We classified it as lung cyst of bronchial type.

DR. HILL.—Cysts of the lung may be either acquired or congenital in origin. The acquired type is associated with infection, and is not particularly uncommon. Congenital cysts are rare. There is confusion about the terminology which should be used for the congenital type. For instance, Caffey[1] states that congenital cystic lung dis-

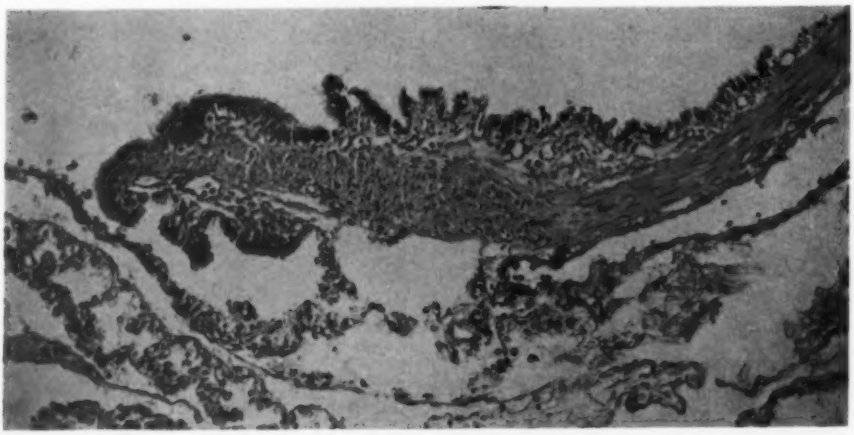

Fig. 4.—Low-power photomicrograph of cyst wall showing bronchial epithelium and muscularis mucosa.

ease has not been found at necropsy at the Babies Hospital in New York in a period of fifty years. He suggests that bronchial obstruction with a check-valve effect leading to acquired emphysematous cavities is the underlying cause in many cases roentgenographically simulating lung cysts. If this is so then congenital bronchiectasis might be the better term to describe the lesion in our patient.

On the other hand, Gross,[2] reported congenital cystic lung disease in a 3-week-old infant, and described histological findings in the cyst almost identical with ours. Such findings, he states, positively identify the cyst as being congenital in origin.

FOLLOW-UP NOTE

This baby is now 6 months old. He weighs 15 pounds, 12 ounces. Breathing is at a normal rate, and the paroxysmal cough has entirely disappeared. Postoperative pleural effusion which was present for a time has cleared and his roentgenogram is that of any normal child. Lobectomy in this instance resulted in a highly satisfactory outcome.

Case 2. Tetanus

DR. JOHN GUSTAFSON (Assistant Resident).—This 6-year-old white boy came to the hospital with complaints of swelling of the right side of the neck and stiffness of the neck and back. He had been well until eleven days prior to admission. At that time he inserted a twig into the right ear. A few hours later pieces of the stick were removed by the family physician, and penicillin was administered. Tetanus toxoid or TAT was not given. For several days there was a purulent discharge from the ear. This disappeared without further therapy and the child was well until two days before admission. At this time he had stiffness and soreness of the right side of the neck and back. In spite of these complaints, he rode his bicycle. On the day of admission, the boy was said to have suddenly "stiffened out all over," and the head was momentarily pulled to the right.

Past history revealed the boy had received tetanus immunization during infancy. Booster injections had not been given, however. Physical examination revealed a well-developed, well-nourished, white boy lying with his head tilted to the right and with his extremities held rigidly in extension. Temperature was 100° F. Sensorium was clear. The right external auditory canal was filled with purulent material. The anterior cervical nodes were palpable bilaterally. Trismus was present and there was rigidity of the abdominal musculature. Reflexes were hyperactive. The remainder of the examination was normal.

Examination under ether anesthesia revealed some fragments of wood in the middle ear. These were removed by an otolaryngologist.

Laboratory studies revealed the following. Spinal fluid normal in appearance, pressure, manometrics, and cell count; no growth on culture. Hemogram: red blood count 4.25 million, hemoglobin 12.0 Gm., white blood count 11,600, with 69 neutrophiles, 24 lymphocytes, 1 eosinophile, 6 basophiles. Urinalysis: Sp. gr. 1.007, pH 7.0, acetone positive, albumin trace, sugar negative, microscopic negative. Serology: negative. Smear of material from ear: white blood cells and many gram-positive diplococci. Culture of material from ear: alpha-strepto-

coccus and *Escherichia coli;* no *Clostridium tetani.*

The boy was placed in a dark room and started on 200,000 U. penicillin every three hours and sedated with phenobarbital. He was given 60,000 U. of TAT. The first day of hospitalization was uneventful and he was able to take fluids orally. On the second day, the pulse and respirations were irregular and increased in rate. There was generalized twitching and marked sweating. On the third day, the temperature rose to 100.6° F., and he refused nourishment. The muscular twitching increased and two generalized convulsions occurred. Opisthotonus appeared and became almost continuous.

His pharyngeal and oral secretions began to accumulate and frequent suctioning was required. Oxygen was administered and phenobarbital sodium was given intramuscularly. In addition, the rectal administration of Avertin, 100 mg. per kilogram of body weight as an initial dose, was started every four hours. Hydration was maintained by parenteral fluids. On the fourth day, three severe generalized convulsions occurred in spite of Avertin every four hours. Generalized rigidity and opisthotonus were present intermittently. Copious amounts of thick oral secretions necessitated the continued use of suction. Convulsions continued throughout the next day. The boy's respirations were shallow and irregular. On the seventh day there was marked restlessness. Dyspnea was present, and laryngeal stridor appeared for the first time. Convulsions were frequent in spite of eight doses of Avertin and the generous use of Sodium Amytal and phenobarbital sodium.

Because of the accumulation of oral and pharyngeal secretions, the presence of laryngeal stridor, the episodes of apnea and cyanosis and the irregularity of respirations, a tracheotomy was performed. Repeated episodes of rigidity and opisthotonus were noted during the day; however, there were no generalized convulsions.

The next day the boy appeared to be more relaxed although he was somewhat restless at times. He was able to swallow his secretions. Coughing was present, and sweating continued. The temperature reached a peak of 103.8° F. Avertin and phenobarbital sodium were continued. Tube feedings were started, and aspirin was given to control the temperature. Chloromycetin was started.

The remainder of the hospital course was one of progressive improvement. By the tenth day the boy was eating. On the twelfth day he was reading comics. We plan to remove the tracheotomy tube in a few more days and send him home.

DR. HILL.—I believe Dr. Byrum has prepared a few comments from the literature about tetanus.

DR. BYRUM (Resident in Pediatrics).—The mortality rate from tetanus during the Civil War was from 90 to 95 per cent. With the advent of TAT, before World War I, it was from 40 to 80 per cent. During World War I it was from 20 to 58 per cent. In World War II there were only eleven cases among eleven million men in uniform. Of these eleven cases, six had had no prophylaxis to tetanus. There were four deaths. Two of these four had not been immunized and two had not received boosters. The present-

day mortality rate is around 30 per cent.

Most of the discussion which I have on the treatment of tetanus comes from an article by Tucker and Lasseter.[3] In tetanus, death is usually due to one of five causes: (1) a spasm of the glottis, of the diaphragm, and the intercostals causing asphyxia and death; (2) pulmonary infection, pneumonia, etc.; (3) a toxic encephalitis; (4) exhaustion; (5) medullary failure. The authors direct treatment toward these complications. They advise radical excision of the wound of entry under Pentothal anesthesia. The circulating toxin is neutralized with antitoxin. They recommend high doses, 100,000 units of TAT, intravenously, each day for three days. Subsequent dosages depend on how well the wound was excised. Spaeth recommends 60,000 units and states that this provides an adequate titer of TAT to counteract the circulatory toxin in the blood stream during the first two weeks of the disease. Sedation is accomplished by placing the patient in a cool, dark, quiet room, and through the use of drugs. Avertin 60 to 100 mg. per kilogram is an excellent sedative. It acts in ten to fifteen minutes and lasts one to three hours. Paraldehyde and chloral hydrate have been used with poor effect. Sodium Amytal, a barbiturate of moderate duration, in a 5 mg. per kilogram dose produces relaxation. It should be given intravenously and in laryngeal spasm. Procaine and Avertin together are superior to Avertin alone.

Recently, Myanesin, a curare-like compound, combined with phenobarbital has given satisfactory control of spasm. Curare has given good results in the hands of some. However, its use is fraught with danger. Sudden death may occur from respiratory paralysis or bronchial spasm. Bronchial hypersecretion may result in drowning the patient. Antibiotics are used to prevent secondary pulmonary infection. Early tracheotomy is recommended to prevent upper respiratory obstruction and to facilitate removal of secretions. In spite of the best sedation, laryngospasm may be unavoidable. Oxygen should be given through the tracheotomy tube under positive pressure. Frequent suction to remove mucus and frequent changes in position help combat pneumonia.

DR. HILL.—Fortunately, tetanus is not of frequent occurrence. We have had only five cases in this hospital in the last four years. Two of them were mild and the patients recovered without incident. The third case was a 15-year-old boy who died in a spasm while we were attempting to do a bronchoscopic aspiration because of atelectasis of the left lung. The fourth case was moderately severe, but the patient recovered with the use of Avertin.

We have presented this case today to emphasize two major points. The first concerns the present method of use of tetanus toxoid. This child had received primary tetanus immunization. Booster shots had not been given before or at the time of injury. This raises the problems as to how long one can expect an effective serum antibody level after the administration of tetanus toxoid and what time is required for a booster dose of tetanus toxoid to induce a protective antitoxin titer in the blood stream. In answer to the first problem there is evidence which suggests protection for less than a year to as long as five years

after primary immunization. There is evidence that if a booster is given within a year after the administration of tetanus toxoid, a subsequent stimulating dose of tetanus toxoid will immediately restore the level of antitoxin to an effective level. More recently, Banton and Miller,[4] in a small series of cases, found that none of the antitoxin titers after a booster dose started rising before the fifth day, and that all were levelled off or checked by the tenth day. They concluded that the rapidity of the response depends upon the residual titer of antitoxin.

Not long ago it was believed that if a person had once had tetanus toxoid, the mere growth of tetanus organisms in a wound would stimulate the production of tetanus antitoxin. Obviously that did not occur in this child, at least in sufficient quantity to afford protection. All this emphasizes the necessity of booster injections following tetanus toxoid, and the use of a booster again at the time of injury.

DR. THISTLEWAITE (Resident).—Is it not true that fluid toxoid, for recall purposes, raises the antibody titer to protective levels more quickly than does alum-precipitated toxoid?

DR. HILL.—Yes, that is so. It is probably also wise in severely lacerated wounds, especially when it has been some time since tetanus toxoid has been given, to give simultaneously a prophylactic dose of TAT and fluid toxoid, but in different locations.

The other point I wanted to mention is the use of tracheotomy in tetanus. I think there is no doubt that it may be lifesaving in some cases. But the difficulty comes in deciding when in the course of the disease to do it. If we wait, as we did here, until muscle rigidity and spasms are severe, the technical difficulties of doing a tracheotomy are greatly increased, and besides one runs the risk, in the meantime, of losing the patient from laryngospasm. This child had three severe prolonged convulsive episodes, one of them coming on ten minutes after Avertin, in which cyanosis and apnea of several minutes' duration occurred. Death could have taken place in any one of them, and nearly did. I think we would have been wiser to have done an early or prophylactic tracheotomy on this boy on the day of admission or at least on the second day.

The other major reason for doing a tracheotomy is to prevent pulmonary complications. Patients who are maintained under deep anesthesia for prolonged periods become oblivious to their bronchial secretions. Respiratory obstruction with respiratory acidosis and anoxia supervene, and death may result. This happened to our 15-year-old boy. A tracheotomy tube in place not only provides the means for keeping the airway open, but also for the adequate administration of oxygen.

Case 3. Transfusion Reaction—Dangerous Universal Donor

DR. MARY PUCCI (Assistant Resident).—This patient, a 6-week-old white female infant, was admitted because of diarrhea and vomiting. Birth had been spontaneous at term and the neonatal period was uncomplicated. Following discharge from the hospital on bottle feedings, the baby had frequent episodes of yellow liquid stools varying from six to ten daily. In spite of this, weight gain continued. During the week prior to admission the baby had a bout of liquid stools. On the day preceding admission most

of the feedings were refused and the child vomited three times.

The only abnormal finding on physical examination was mild dehydration. Laboratory studies revealed a normal urinalysis, red blood count 2.9 million, hemoglobin 9.9 Gm., and white blood count 14,800 with 33 neutrophiles and 52 lymphocytes. A smear of the peripheral blood showed normochromia, mild microcytosis, and moderate anisocytosis. Rh was positive. Serology was negative.

The child was given protein milk. As the intake was adequate and fairly well tolerated, parenteral fluids were not administered. The stools, although never numerous, were liquid and green. Several small regurgitations were noted after some of the feedings. By the third day this had ceased, and the stools assumed a more normal appearance. Alternate feedings of Olac and protein milk were offered. By the sixth day there were no further gastrointestinal symptoms. To correct the anemia, 90 c.c. of whole blood, Group O, Rh positive, were given over a period of two and one-half hours. There was no evidence of incompatibility during the transfusion. However, one and one-half hours after it was completed, red-brown urine was noted and this persisted for twenty-four hours. Urinary output remained good as indicated by thirteen red-brown-stained diapers. Diarrhea again appeared and the baby passed twelve liquid green stools. Jaundice developed and the baby appeared to be seriously ill, with pinched facies and sunken eyes. The liver became palpable 3 cm. below the right costal margin. The temperature rose to 103.2° F. Parenteral fluids, oxygen, and penicillin were administered. Molar lactate was given orally in an effort to alkalinize the urine. Eighteen hours after the onset of the hemolytic reaction, laboratory studies showed red blood count 3.6 million, hemoglobin 12.0 Gm., and white blood count 20,950. Twenty-four hours after the onset, the laboratory findings were red blood count 2.9 million and hemoglobin 9.3 Gm. Urine gave a positive reaction for blood. A smear of the peripheral blood showed spheromicrocytosis and polychromasia. Normoblasts were present.

During the second twenty-four hours following the transfusion the urine production was good. The color gradually cleared to a pale pink. The diarrhea stopped. Jaundice faded and the liver receded to 2 cm. below the costal margin. The tip of the spleen became palpable. Nutrition and hydration were maintained by the oral and subcutaneous routes. The child made a rapid recovery. On the fourth day icterus was no longer present and the physical findings were normal except for pallor. The hemogram showed: red blood count 2.3 million, hemoglobin 6.3 Gm., white blood count 11,750. The blood smear showed 2 normoblasts per 100 white blood cells.

DR. HILL.—This sounds like a case of blood miss-matching. Was the cross-match investigated?

DR. PUCCI.—Yes, it was. The donor blood was taken from the bank. It was Group O, Rh positive, and had been drawn three days prior to administration. Originally, only the major cross-match (donor's cells with patient's serum) was done, as this has been the custom in this hospital where Group O blood is routinely used in young infants. Likewise the blood group of infants under 6 months of

age is not determined. Using blood samples which had been drawn before the transfusion, the laboratory typed the child as Group A, Rh positive. Repeat major cross-matching showed compatibility between the donor's cells and the patient's serum. Because of hemolysis of the patient's cells which had been standing for several days, the minor could not be carried out.

DR. HILL.—This begins to sound a bit more complicated. Dr. Birge, can you enlighten us as to what happened?

DR. R. F. BIRGE (Pathologist).—A blood smear taken on the day following transfusion showed spheromicrocytosis with polychromasia, normoblastosis, and neutrophilic left shift. Spheromicrocytosis was striking by the second day following transfusion when the leucocyte count was 22,000 accompanied by pronounced left shift. Erythrocyte fragility was increased. The blood picture was that of hemolytic anemia.

The first question that arose was: Does the patient have familial hemolytic anemia with hemolytic crisis precipitated by blood transfusion? The patient's pretransfusion smears were reviewed, and her anemia was found to be normochromic in type. Microcytosis was minimal. The parent's blood smears showed no microcytosis. All three individuals were found to be Group A, Rh positive. Hemolytic anemia of the newborn seemed to be ruled out. There was no pretransfusion clinical or laboratory evidence for naturally acquired acute hemolytic anemia. The Coombs test was negative. Cold and autoagglutinins were not present.

The phenomenon of spheromicrocytosis which appeared so rapidly was puzzling because one does not see this response in the usual hemolytic transfusion reaction incited by administration of incompatible donor erythrocytes. However, Dr. Nielsen learned that such a picture may be observed in so-called dangerous universal donor transfusion reactions in which the usual cause of hemolysis is infusion of anti-A agglutinins into Group A recipients. Perhaps Dr. Nielsen will comment on this point.

DR. GLEN NIELSEN (Resident).—Young, Ervin, and Christian[5] state that spheromicrocytosis and increased red cell fragility were observed in all cases of transfusion reactions resulting from the giving of Group O blood with high anti-A antibodies to Group A recipients. The spheromicrocytosis was transitory, lasting from nine to eighteen days. I know of no other type of transfusion reaction which causes this phenomenon.

DR. BIRGE.—When the infant's blood grouping was rechecked, using blood drawn before transfusion, the infant's *erythrocytes* showed weak agglutination with anti-A typing serum, but the infant's *serum* would not agglutinate Group A or B cells. After transfusion, the infant's *serum* strongly agglutinated Group B cells.

We could now theorize that Group O blood of high agglutinin titer probably had been given. Donor anti-A agglutinins had been absorbed by the patient's erythrocytes producing the morphologic changes previously described. Furthermore, the foreign anti-B agglutinins were still present in the baby's serum as demonstrated by the change in the blood grouping response.

On checking the donor blood, we obtained a titer for anti-A agglutinins of 1:1,024, and for anti-B agglutinins of 1:2,048.

This is the first transfusion reaction due to use of Group O blood that has been recognized in over six years of operation of our Blood Bank. It is our practice to limit intergroup transfusion as much as possible. However, in infants we are never sure of our blood grouping work, and here we customarily administer Group O blood. We have not added Witebsky A and B substances because of the advice of good authority that it is probably not necessary. Whether or not use of the substances would have prevented this transfusion reaction is problematic, but we shall probably use them in the future if only for medicolegal reasons. We must, of course, review our laboratory practice. It would seem advisable to do screen titrations of all Group O donors, reserving Group O blood showing titers for anti-A or anti-B agglutinins of perhaps 1:200 or higher for intragroup transfusions.

Besides the lessons that this case has for the laboratorian, an important consideration from the clinical point of view needs emphasis. There is always a 3 to 4 per cent risk that some sort of reaction will occur with transfusion. Fatal hemolytic reactions occur in the best of medical centers where blood transfusion work is supervised by full-time hematologists.

One authority has recently stated that the mortality of blood transfusion is equivalent to that of appendectomy in uncomplicated cases!

Dr. Henry Corn.—How frequently does one find dangerously high titers of anti-A and anti-B agglutinins in Group O blood?

Dr. Birge.—Very seldom, for severe reactions of the type we are discussing are uncommon, and rarely if ever eventuate in death.

However, it seems probable that mild reactions due to administration of high titer Group O blood must occur with moderate frequency, although seldom recognized clinically. Many such recipients will show post-transfusion elevation of the serum bilirubin, doubtless a consequence of destruction of recipient erythrocytes. One may largely prevent this occurrence, according to Strumia and McGraw[6] by screening Group O donors in the manner that I mentioned a moment ago. About 25 per cent of Group O sera will agglutinate A or B erythrocytes in dilution of 1:200. One considers such donors to be "dangerous" and reserves their blood for intragroup administration.

Dr. Jack Spevak.—What can be done if the baby needs more blood?

Dr. Hill.—Since this is a patient of yours, Dr. Standefer, perhaps you would like to answer that question.

Dr. J. M. Standefer.—There are three possibilities. Washed Group O red cells, resuspended in saline, can be used. Group O blood low in anti-A and anti-B agglutinins could probably be used safely, and as an added precaution Witebsky's substance could be added. The third possibility is to transfuse Type A blood, but there is the slight risk of further hemolysis as a result of the previously injected anti-A agglutinins.

FOLLOW-UP NOTE

It became apparent that another transfusion was indicated. After much deliberation 90 c.c. of Group O,

Rh-positive blood containing low titers of anti-A and anti-B substance was administered. Soluble A and Soluble B substance was added for further protection. There were no untoward effects. The hemogram following this was: red blood count 2.5 million, hemoglobin 8.0 Gm., white blood count 12,500. Thirteen normoblasts per 100 white blood cells were seen on the smear. A third transfusion of 90 c.c. from the same source as the second was given with marked improvement in the hemogram: red blood count 3.5 million, hemoglobin 11.0 Gm., white blood count 8,500. The peripheral blood contained 3 normoblasts per 100 white blood cells. Although decreased in number, spheromicrocytes persisted. Polychromasia was less.

The child was discharged from the hospital as recovered twenty days after admission. Final diagnosis was transfusion reaction due to blood from a "dangerous universal donor."

Case 4. Waterhouse-Friderichsen Syndrome (?) With Recovery

DR. REED FIFE (Assistant Resident).—This patient is a 20-month-old white girl. She was admitted to the hospital in the late afternoon of Aug. 9, 1950, because of (1) rapid breathing of one to two hours' duration, (2) blueness of the lips which had come on simultaneously with the rapid breathing, (3) stupor which had steadily increased during the afternoon until the parents were unable to rouse her, (4) a "rash" over most of her body which had developed during the day, and (5) fever, which had been present most of the day.

Family, birth, and past history were noncontributory to her present illness. Four days before admission she developed a cold, and the day before admission she had several watery stools. She slept well that night but did not seem as well the next morning. She vomited several times and appeared feverish. She ate some ice cream, however, and wanted water frequently. The parents did not become alarmed until mid-afternoon when the breaking out on her body became more noticeable, and the rapid breathing, cyanosis, and stupor occurred. She had eaten some artificial flowers the day before, but so far as was known she had not swallowed any poisons, nor had she been given medicines of any kind, including aspirin.

Her rectal temperature on admission was 106° F. She appeared to be in shock, deeply stuporous, with grayish pallor of her skin, cyanotic lips, and a weak pulse. The "rash" consisted of numerous petechiae generally scattered over her body interspersed with larger ecchymotic areas. Petechial hemorrages were noted in the conjunctivae and in the mucous membranes of her mouth and throat. There was slight stiffness of the neck, and Kernig's sign was mildly positive. Otherwise the neurological examination was negative. No masses could be felt in the abdomen although palpation was done with the possibility in mind of hemorrhage into the adrenal glands. The remainder of the physical examination yielded no additional information. Respirations were 60 per minute, and the pulse rate was 150.

Laboratory findings were as follows: red blood count 3.36 million, hemoglobin 9.3 Gm., white blood count 25,550, lymphocytes 29 per cent, polymorphonuclear leucocytes 42 per cent, band cells 29 per cent. Carbon dioxide combining power was 27 volumes per cent. A lumbar puncture showed

clear fluid with 31 cells of which 75 per cent were lymphocytes and 25 per cent were neutrophiles. Spinal fluid chloride was 666 mg., glucose 66 mg., protein 18 mg. No bacteria were seen on direct smear of the spinal fluid. Urinalysis was negative. A blood culture was made and *Neisseria intracellularis* was later identified.

Because of the rather characteristic clinical picture, the immediate impression was fulminating meningococcemia —probably Waterhouse-Friderichsen's syndrome, and early meningitis. The child was placed in an oxygen tent, and intravenous fluid administration begun. This consisted of ⅙ molar lactate, followed by lactate Ringer's and glucose solutions. Aqueous penicillin, 1,000,000 units, was given intravenously, initially, followed by 1,000,000 units intramuscularly every two hours. Ten cubic centimeters of adrenal cortical extract were given intramuscularly every hour for four doses; 5 c.c. every hour for two doses; then 1 c.c. every hour for seventy-two doses.

By 8:00 A.M. the next morning the temperature had dropped to 98.2° F. rectally. The child's pulse was still rapid but was much stronger and her color had improved. She was much less stuporous and would object when disturbed. Later in the morning her temperature rose to 101.8° F. and a new crop of petechiae was noted over the entire body. A repeat lumbar puncture was done which showed 273 cells with 75 per cent neutrophiles and 25 per cent lymphocytes. Spinal fluid chlorides were 643 mg., glucose 129 mg. (probably due to parenteral glucose administration), and protein 18 mg. An equal mixture of sulfadiazine and sulfamerazine was started subcutaneously, 0.3 Gm. per kilogram the first eight hours, 0.2 Gm. per kilogram in the next eight hours, then 0.1 Gm. per kilogram each eight hours. The urine was kept alkaline with molar lactate. A peak blood sulfa level of 27.6 mg. per cent was attained. Sulfa therapy was continued for five days.

The temperature dropped rapidly again and remained normal. The second crop of petechiae disappeared within two days without ulceration. However, the original petechiae became black and necrotic and sloughing occurred in the centers. All parenteral fluids were discontinued on the sixth hospital day, and the 1,000,000 units of penicillin every two hours was reduced to 25,000 units every three hours. In forty-eight hours this was replaced by daily injections of 300,000 units of the long-acting penicillin. All therapy was stopped by the tenth day and she now appears to have made a complete recovery with the exception of the cutaneous ulcerations.

DR. HILL.—I saw this child shortly after she came into the hospital and she differed in no way in her clinical appearance from other children I have seen in the past with Waterhouse-Friderichsen's syndrome who died, and at autopsy showed bilateral adrenal hemorrhage. It is difficult to say whether it is the acute adrenal insufficiency or the toxemia and infection which plays the dominant role in these cases. So far as I can recall this is the first patient at this hospital to recover from Waterhouse-Friderichsen's syndrome—if that is what this child had. However, it is the first time that this particular therapeutic approach has been employed. Dr. Burr, would you comment about the massive doses of penicillin you used in this patient?

DR. CHARLES BURR.—I believe it was Dr. Harry Gordon of Denver, when he was visiting us a couple of years ago, who first drew our attention to the report of Dowling and associates[7] recommending 1,000,000 units of penicillin every two hours for the treatment of pneumococcus meningitis. The authors also recommended this form of therapy in fulminating meningococcemia. Not long ago I employed this method of treatment for a 3-month-old infant with pneumococcus meningitis, and the baby made a very satisfactory recovery. It seemed logical to give it a try in this case. Naturally, a series of one patient does not prove much, and it must be admitted that smaller doses of some other drug might have been equally effective.

DR. HILL.—Dr. Fife, do you want to express your opinion about classifying this case as one of Waterhouse-Friderichsen's syndrome?

DR. FIFE.—By definition, the syndrome includes, in addition to the clinical picture as seen here, massive bilateral adrenal hemorrhage. The presence or absence of the hemorrhage cannot be proved in this case.

The exact pathogenesis of the signs and symptoms of meningococcemia are not known or agreed upon by all investigators. Kinsman and collaborators[8] describe cases similar to this one in which the primary changes were thought to be degeneration of the cortical cells, probably due to overwhelming toxemia—actual hemorrhage into the adrenals was thought to represent an irreversible end stage in the degeneration of the gland and may or may not be responsible for the clinical picture. Cortical degeneration was present in all the cases which came to necropsy, but hemorrhage was not a uniform finding. When recovery occurs, the pathological changes in the adrenals, as well as in the remainder of the body, are temporary and reversible. It does not seem logical that massive adrenal hemorrhage would permit early restitution of normal adrenal physiology. I believe the Waterhouse-Friderichsen's syndrome should remain a pathological diagnosis.

DR. HILL.—I am inclined to agree with you. I think it is clear that massive bilateral adrenal hemorrhage is not necessary in the pathogenesis of the fulminating shocklike picture these patients present. This was illustrated in another child we have recently seen who came to the hospital in shock after a few hours' illness, with a rectal temperature of 108° F. There was no rash. The child lived only an hour or so after admission. Klebsiella organisms were recovered from both the blood and the spinal fluid. No hemorrhage was found in the adrenal glands but marked necrosis of cells was evident at histological examination.

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Psychologic Aspects of Pediatrics

THE PEDIATRICIAN AND HIS ROLE IN UNDERSTANDING CHILDREN'S BEHAVIOR

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THE practice of pediatrics is changing. More and more of the pediatrician's time is being spent with well children. In his medical education, the emphasis has been on pathology and he has had little or no training in the understanding of the well child, which is the root of his present dilemma.

By the same token we find ourselves in an era where the psychology of children's behavior is a very fashionable topic. It is almost impossible to pick up a current magazine or newspaper without finding some articles on the do's and don't's of child rearing. These articles have a strong appeal to parents, who are trying their best to bring up their children sensibly. It does not take them long to discover that the advice they get from these sources is conflicting. One week they are advised to do one thing; the next week, another. They end up with a very understandable sense of confusion. In the past, when they have been in doubt about their child's physical well-being, they have been in the habit of seeking advice from their physician. Today, they are turning more and more to their pediatrician for guidance in rearing their children according to the best knowledge available from scientific studies. The day has passed when they can accept, confidently, the well-meant remark of the physician who says, "Don't worry, he (or she) will grow out of it."

The pediatrician is well aware of his own importance in this new role. Teaching hospitals and postgraduate educational sources are being called upon to supply a sound body of information about the average child's behavior and emotional needs. The practicing physician is eager to substitute an objective unbiased knowledge about children's emotional development for his hitherto personal deductions.

In the face of this demand from the private physician for a teaching of the basic concepts of the behavior of normal children, the Division of Child Development in the Department of Pediatrics at The New York Hospital has set up a training program in this field as a part of the routine experience of the young pediatrician-in-training. Exactly how to teach most effectively normal emotional growth and development to pediatric personnel is in a stage of evolution in medical education. This paper is a report of just one way of doing it, which has brought encouraging results. The teaching is based on three fundamental parts: (1) a series of orientation lectures; (2) a nursery school experience, and (3) rounds and seminars on the child in the hospital.

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It was felt that there is a basic body of knowledge about children's behavior that has to be understood by the pediatrician before he is capable of evaluating the average behavior of children. For this reason, an orientation lecture course in the emotional growth and development of children from infancy to adulthood is given. In this series of lectures an attempt is made to say what a growing child is like in simple, clear English without the use of psychologic or psychiatric terms. We try to show that the emotional needs and responses of children, which are the key to their behavior, differ from one stage of development to the next. The stages of development are broken down into five areas, which are already known to the pediatrician. The first is infancy. The infant is more different now than he will be at any other time of his development and his needs are likewise distinct. The second stage is that of the toddler who has become ambulatory, but whose need of and dependency upon the mother is so great that he still has to be thought of in partnership with her. The third stage, the preschool child, has more physical independence but is greatly limited in experience. As he explores the enlarging and exciting world around him he demonstrates beautifully the wide gamut of emotional response and his own vulnerability. The fourth stage, the school child, is completely different from the preschool child in his greater understanding of facts, which helps him to deal with the confused ideas of the world he had in his preschool years. Finally, the fifth stage is the adolescent, whom medicine has traditionally treated as a special person vacillating between childhood and adulthood and belonging to neither. An acquaintance with this basic material is the first fundamental part of this program.

As this theme of normal emotional growth and development from infancy to adulthood is outlined to the pediatric staff, the behavior of the children on the wards affords illustrative material. These lectures and illustrations do little more than provide a common framework for thinking constructively about emotional needs.

It is well known that learning itself is an emotional experience. One learns best when one becomes personally involved with the subject at hand. For this reason, a laboratory for the demonstration of the facts outlined in the series of orientation lectures about children's behavior has been provided. This is the second fundamental part of the program.

This laboratory is a nursery school at The New York Hospital, which is an assigned clinic in the Department of Pediatrics. It is comprised of fifteen average neighborhood children between 2 and 3 years of age, who are physically well and present no outstanding emotional problems. The nursery school has two full-time teachers, well versed in the understanding of a child. In their handling of the children they constantly demonstrate this knowledge in action. Each doctor spends one day a week for three months in the nursery school. He acts, in large measure, as an assistant nursery school teacher and takes active part in the full day's routine from 9:00 A.M. to 3:00 P.M., which includes:

Indoor play	Undressing
Toileting	Washing
Juice time	Quiet play
Dressing for the yard	Lunch time
Outdoor play	Bedtime

For many of our pediatricians, this is their first experience with a group of well children. Their total training has been with the sick child. In the nursery school, their medical skills and knowledge of pathology are not needed, and the relationship which the doctor forms with the child is based largely on his understanding of that child. It must be said that no doctor has gone to the nursery school without the feeling that he would like to be kind to the children. It also has been found that it is impossible, *at first,* to teach him much about a child when things are going pleasantly. It not infrequently happens that on his first day a child will sit on his lap and demand his attention. Without exception, the relieved expression on the young doctor's face is one of: "This doesn't surprise me at all; I am irresistible to children." Undoubtedly, the doctor who in this setting is the "stranger in the house" is as comforted by this performance as the child himself. However, he has little understanding of the genuine sincerity of the child's action in this pleasant situation until he has had the benefit of an experience with the equally sincere negative reaction of a child. It is just a matter of time before he will be plunged into that learning experience. Quite frequently the very child who demanded attention will later stand up in front of him and say, angrily, "I don't like you—go away!" There is no mother on hand to apologize or to say that the child does not mean it, as might happen in his consultation room.

By and large, the doctor's reaction breaks down into two kinds. The more sensitive doctor backs away from the child, defeated. He is likely to say, "I don't know what happened, and I certainly don't know what to do about it. If it weren't so ridiculous, my being so big, and the child being so little, I would say that my feelings were hurt. What should I have done?" When this happens, real learning begins because the doctor is emotionally involved in the situation. The lecture material takes on personal meaning for him. The other kind of response is that of a more determined doctor, who does not believe his ears and tries to insist that the child obey in spite of objections. It is sheerly a matter of time before he, too, retreats for a conference. Only when this has happened, can the doctor begin to see that the nursery school teachers' friendly, calm, fair, and consistent attitude to the child is a technique. Only when he, too, learns how to handle the negative relationships with a child can he fully appreciate a good relationship.

In addition to the actual experience of each doctor in the nursery school with the children, we try to make as full use of the nursery school as possible in other ways. He attends nursery school staff conferences where a small group discusses very informally the behavior of individual children in the school. At nursery school seminars he hears invited outside authorities in the field of child development discuss various aspects of a child's behavior. He is invited to attend a monthly parents' meeting, which is under the leadership of a member of the nursery school staff. He listens to the spontaneous discussions of the parents of the nursery school children of common, everyday problems regarding the handling of their children. He recognizes

that the parents' questions are no different from those he has asked himself in his supervisory conferences. It is reassuring to him to have shared these same perplexities, as well as to hear the now familiar suggestions that are made by the nursery school staff. These answers are becoming a part of his own working techniques with children. He recognizes that here lies the groundwork for the guidance that he will give in the future in his private practice to parents who ask these same questions. Also from his experience in the nursery school he gains a certain sense of confidence in his ability to deal directly and simply with the child himself, which can be one of his most valuable tools in the practice of pediatrics.

The third basic part of the program involves the child in the hospital. In the rotation of house officers through the nursery school, we all meet again on the pediatric floors. Each week, rounds are made throughout the children's pavilions so that every child is known to us. In the past, the pediatricians have referred most frequently two kinds of patients for emotional evaluation. At one extreme was the mentally retarded child, and at the other, the obviously psychotic child. With the development of the program being described in this report it has been very interesting to note the change in the pediatrician's referrals. With the mentally retarded child, the pediatrician thinks in terms of proper institutional care for the child while he plays an active supportive role to the parents in their decision for placement. With the frankly psychotic child, the pediatrician refers him promptly to Child Psychiatry. The greatest share of our time is then given to the average child, who happens to be hospitalized for one reason or another. A clinical evaluation of the behavior of these children is based on the knowledge of his normal emotional needs, according to his age level, his own particular life experience, and the meaning of his illness to him.

The nursery school has taught many lessons, which the doctor has been able to make use of in his care of the sick child. One example is this: The pediatrician has found that the well 2- to 3-year-old child in the nursery school is verbal. When that same 2- to 3-year-old child is hospitalized, the pediatrician has become used to a silent child. Frequently, if a person does not speak it is assumed that he does not understand. The attitude of the pediatrician, after his experience in the nursery school, toward this sick child is almost as if he said, "You may not speak but I know you understand." He realizes that speech or no speech, he can talk to a listening child about the procedures he must do, and he is not surprised to find a silent understanding and cooperation on the child's part.

Many a leaf has been torn from the nursery school experience and applied in our Occupational Therapy Department, which has become in a sense like a nursery school for the sick child. In the total treatment of the child, the house officer, who has worked through the nursery school experience, is now eager to get the sick child to Occupational Therapy where he will be exposed to the type of handling that the house officer has seen work so well in the nursery school with the well child. For example, on a thirty-bed ward one day there were only two patients; one was in coma, and the

other was coming out of ether. Every other child was in our Occupational Therapy Department, busily engaged in his own project.

It may be worth while mentioning that the whole concept of group entertainment for children in Occupational Therapy has been abandoned. Each child, according to his own age level with its specific interests and abilities, has a choice of materials and play equipment that we know appeal to him. The occupational therapists are there to suggest and help, if the child wishes, in any activity of his own choosing.

In addition to ward rounds, there are informal seminars on the hospitalized child. Here it is possible to correlate the behavior of the sick child with what we understand from the orientation lectures and with our living experience with the well children in the nursery school. The seminars are not limited to a case presentation. A free discussion between all members of the staff on any phase of children's behavior is encouraged. The individual doctor's growing ability to talk about emotional attitudes and evaluate them clinically is well demonstrated in these seminars during the course of an academic year.

It is our belief that this type of understanding of a child belongs to no special group but rather should be the common property of all people who deal with children. In our own hospital, there are five professional groups who have responsibilities to the sick child. These are the doctors, the nurses, the social service workers, the occupational therapists, and the medical students. The same three fundamental activities of orientation lectures, nursery school experience, and seminars with the sick child are offered to all of these professional groups. This means that although the individual professional responsibility to the child differs widely, this type of teaching has made possible a common approach of all these different personnel to the child.

One of the secondary gains to this common understanding of the child, which is shared by all pediatric personnel, has been the ease with which many hospital procedures have been modified to meet the needs of the child. As for example, all children over 2 years of age needing surgery, without severe anemia or congenital heart diseases, routinely receive a rectal anesthesia in their rooms in the presence of their mothers, so that they go to the operating room asleep and have no memory of an ether mask or being forcibly separated from the mother; mothers may remain with their children until they are awake, after surgery; elective hospital admissions are postponed if a new sibling has arrived in the family; no attempt is made to wean or to toilet-train a hospitalized child; visiting times for parents can be arranged to meet the needs of the individual child, etc.

It is our feeling that the pediatrician who has had the benefit of this type of teaching experience, in his regular pediatric training, will find himself able to meet in his private practice the growing need on the part of the parents for sound and wise guidance of their well children. His deeper understanding of the child and his confidence in his ability to deal directly and simply with the child himself frees him to practice a more satisfying kind of pediatrics. In a literal sense he is truly equipped to treat the total child.

Comments on Current Literature

POLYMYXIN IN THE TREATMENT OF MENINGITIS DUE TO PSEUDOMONAS AERUGINOSA

THE remarkable development of antimicrobial agents within recent years has provided effective therapy for almost all of the common bacterial infections. There are exceptions, however, since in vivo and in vitro studies indicate that certain bacteria are resistant to these agents. An outstanding example of such resistance is *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*). The therapeutic problem presented in the management of infections due to *Ps. aeruginosa* is particularly difficult to handle when the infection is that of the meninges. This subject is discussed by E. R. Hayes and Ellard Yow[1] in a recent report entitled "Meningitis Due to *Pseudomonas aeruginosa* Treated With Polymyxin B."

From a brief review of the literature, these authors point out that infection of the meninges with *Ps. aeruginosa* has a high mortality in untreated cases. Stanley's[2] series, for example, showed a mortality rate of 55 per cent in cases of primary meningeal infection. When meningeal infection resulted from pseudomonas bacteriemia, fatal outcome occurred in 86 per cent of the cases. Of forty-one cases of primary infection of the meninges, thirty-two were attributed directly to the performance of a lumbar puncture, carried out either for diagnostic or for therapeutic purposes. In one instance, the organism was introduced apparently by lumbar puncture which was performed for spinal anesthesia.

Since poor therapeutic results had been reported by others, and since their own patient had failed to respond to the usual therapeutic agents, Hayes and Yow resorted to the use of polymyxin in the treatment of their patient with meningitis.

Polymyxin,* a comparatively new antibiotic, is a polypeptide derived from a strain of soil bacteria, *B. polymyxa* (*B. aerosporus Greer*). This antibiotic has been shown to be highly active in vitro against a wide variety of gram-negative organisms, including *Aerobacter aerogenes, Escherichia coli, Salmonella typhosa, Klebsiella pneumoniae, Hemophilus influenzae,* and *Ps. aeruginosa.* The antibiotic is not effective against *Proteus vulgaris.* Nephrotoxic and neurotoxic side effects of polymyxin have been reported.

Hayes and Yow present in detail the clinical course of a patient with meningitis due to *Ps. aeruginosa.* Their patient, a 17-year-old girl, was first seen with an ill-defined illness which had failed to respond to what ordinarily should have been adequate therapeutic coverage. Subsequently she developed signs and symptoms of meningitis, and the invading organism was shown to be *Ps. aeruginosa.* Intensive treatment with penicillin, aureomycin, streptomycin, and sulfadiazine failed to alter the course of the meningitis significantly. In vitro studies revealed that the organism was extremely sensitive to polymyxin B. The initial course of treatment with polymyxin B consisted of 80 mg. intramuscularly every six hours and 2 mg. intrathecally every twelve hours. After a period of twenty-four hours, the intramuscular dose was changed to 40 mg. every four hours. This therapeutic regime was continued for a period of ten days. The cerebrospinal fluid was free of viable organisms on the day following institution of polymyxin therapy. The organism was obtained again, how-

*Polymyxin (Aerosporin, Burroughs Wellcome & Co., New York.

ever, on culture of spinal fluid obtained seven days after discontinuance of the polymyxin. The patient again became febrile, and polymyxin therapy was reinstituted. This second course covered a four-day period: 40 mg. intramuscularly every four hours and 2 mg. intrathecally twice daily. Again clinical improvement was noted in the patient, and the spinal fluid was shown to be free of organisms.

Eleven days after antibiotic therapy was discontinued, *Ps. aeruginosa* was cultured once more from the spinal fluid, and a third course of polymyxin B was initiated. The dosage scheduled consisted of 40 mg. intramuscularly every six hours and 2 mg. intrathecally once daily. After four days, the intrathecal therapy was discontinued because of central nervous system irritation as evidenced by pain in the legs and back. The intramuscular administration was continued for sixteen days.

Following the third course of polymyxin, the patient continued to improve, and the spinal fluid remained free of organisms. Seven months following therapy, the patient had regained her original weight and "felt well in all respects." No neurological abnormalities have been noted, except for mild hearing loss of the nerve type.

Nausea and vomiting which were associated with polymyxin administration were controlled with remarkable success by the administration of Pyribenzamine.

Since meningeal infection with *Ps. aeruginosa* may occur secondary to spinal puncture, the absolute necessity for strict aseptic technique in performing this routine procedure is obvious.

The authors call attention to the gravity of meningeal infections due to *Ps. aeruginosa*, and conclude that, while this antibiotic in its present form must still be regarded as a dangerously toxic drug, "evidence available at the present time indicates that polymyxin is superior to any other drug in the treatment of infections due to *Pseudomonas aeruginosa*."

Careful clinical evaluation carried out under rigidly controlled conditions will be necessary before assigning polymyxin B to its proper place in the medical armamentarium.

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News and Notes

Dr. Henry H. Perlman, who has contributed a number of articles to the JOURNAL, was appointed Assistant Clinical Professor of Dermatology and Assistant Attending Dermatologist at a recent meeting of the Board of Trustees of the New York Medical College, Flower and Fifth Avenue Hospital.

The **Third Panamerican Congress of Pediatrics** will be held at Montevideo, Uruguay, Dec. 5 to 8, 1951, following immediately after the Third South American Congress, Dec. 2 to 4. This is the beginning of the summer season in Uruguay. Dr. Conrado Pelfort is President, and Dr. Prof. Maria Luisa Saldun de Rodriguez, Secretary, with offices at Av. 18 de Julio 1246, Montevideo, Uruguay.

Six main subjects will be discussed: (1) Rheumatic Fever, (2) Blood Diseases of Hemorrhagic Tendency, (3) Surgical Treatment of the Congenital Malformations, (4) Parasitary Diseases of Social Importance in the Child, (5) Teaching of Pediatrics, (6) Mental Hygiene and Neurosis in Childhood. Pediatric leaders from Brazil, Argentina, and Uruguay have been designated for the sections. Invitations have been issued to pediatricians in the United States and Canada to participate in the discussions.

Twenty grants have been made beginning July 1, 1951, by the **Markle Foundation** for training medical scientists. This stipend has been increased from $5,000 to $6,000 a year for a period of five years. Included among them are Dr. Robert E. Cooke, resident and instructor in pediatrics, Yale University School of Medicine, and Dr. Howard A. Joos, instructor in pediatrics, University of Rochester School of Medicine. This will make a total of sixty-six grants that have been made since the program was inaugurated.

A six months' fellowship is available at the **Seizure Division of the Children's Medical Center in Boston.** This provides experience in electroencephalography and in the diagnosis and treatment of epilepsy of both office and clinic patients. For additional information, address Dr. William G. Lennox, 300 Longwood Ave., Boston 15, Mass.

Book Reviews

Handbook of Biolinguistics. C. L. Meader and J. H. Muyskens, Toledo, Ohio, 1950, Herbert C. Weller, 330 pages. Price $10.00.

Biolinguistics, according to the authors, is a biological approach to all phenomena of speech in which an explanation of all language is sought in the functional integration of tissue and environment. This book, the first of several volumes, is concerned with the structure and processes of expression used in normal speech. Many fine tables and drawings of the anatomical aspects of speech are included.

The main contents of the book are as follows:

Introduction to Phonetics: Dynamic phonetics is composed of the study of the general characteristics of tissue activity. For a complete understanding of the biological foundations of language, the integrated relationships of the nutritional, muscular, and nervous processes, as well as endocrine functioning and the action of the lymphatics, are essential.

Protoplasm, Cells and Tissues: The living cell as a structural unit of tissue activity is defined and described in detail. Protoplasm possesses properties of excitability or irritability, movement, secretion, growth, and reproduction. The five stages in the development of the human body are: (1) the primitive fertilized ovum, (2) undifferentiated mesenchyme, (3) specialized cells, (4) tissues, and (5) organs. Language begins in the prenatal period and continues to develop

rapidly as the sensory apparatus becomes more refined in its specificity. The normal linguistic function can be understood on the basis of the developmental history of normal structure and functions of tissue. Consequently, abnormal speech can be understood and remedied by interpreting the tissue involved.

Development of Specificity: As the human organism evolves, the tissues and organs develop a specificity of function. The three basic principles of biolinguistics are: (1) energy, the basis of all activity, (2) integration, the interaction of systems of energy and subsequent modification of the organism, and (3) emergence, the arising of a new system which differs quantitatively and in pattern from the original integrations. The evolutions of the "speech organs" and their functions furnish an example of emergence.

Development of Tissues Involved in Speech: The types of cells and tissues of the muscles and nerves involved in speech, their development and specificity, and the functions of the glandular tissue, endocrine glands, blood, lymph, supporting tissues, and nutrition in relationship to speech are presented.

Embryological Development of the Speech Organs: The various organs used in the speech process are described in their embryological development. In addition, the embryology of the pharynx, larynx, diaphragm, etc., is given in vivid detail with drawings.

Integration—Processes of Speech: This section deals with speech as a function influenced and determined by all body activities. The integration of the vegetative processes of the body is described, with particular attention paid to the alimentary process of digestion, respiration, and circulation, as well as the action of the vegetative nervous system related to muscle tonus, glandular secretion, and mental activities. The muscles and nerves involved in these processes are represented in drawings and tables.

Integration—Neuromuscular System: This section explains how the neuromuscular system acts as an integrated mechanism in the production of speech. Specifically, the following processes are described and clarified by excellent drawings: (1) the synergia and classification of "antagonistic" muscles, (2) the specific function of these muscles, (3) inspiration and expiration, (4) the overlapping of many nerve trunks as a mechanism of selectivity, and (5) the control processes of speech through nutrition and hormones, the sympathetic system, and the central and peripheral systems.

Integration—General Principles: The total integration of the organs and tissues of the body during the process of speech is discussed in this section. Many series of simultaneous and successive integrations of systems of process constitute life. The integrations within which language arises are: circulatory, respiratory, and postural activities; valving of the vocal tubes; the concomitant nervous, glandular, and muscular activities of the vital organs of the trunk; and the neuromuscular processes of the somatic, peripheral exteroceptive and motor organs. Furthermore, the environment is involved in these systems. A classification and description of reflexes and the principles of conditioning in relationship to language are presented.

Determinants of Language: The specific influences and integrations of the gross structures and functions necessary for the language processes are listed and discussed, along with the vegetative functions and environmental influences. A chart graphically presents the determinants of the language process.

Emergence of the Speech Process: This section of the book is concerned mainly with how speech developed from lower biological functions. As more specific structures evolved, the primitive organs became more adaptable to the communicative process. The structure of the larynx and the actions of the muscles of expiration during speech are given. The development of speech in five stages (melody, rhythm, accent, vowel, and consonant) is given detailed attention from the viewpoint of the physicochemical processes in the tissues and the active and passive movements of these tissues.

The book is well organized and graphic in its description of the speech process. The medical and educational professions will find it of value for an understanding of the biological backgrounds of speech.

D. KENNETH WILSON

Editor's Column

THE ANTIHISTAMINIC DRUGS AND THE COMMON COLD. II.

SOME eight months ago the JOURNAL discussed editorially the amazing story of the antihistaminic drugs and the conflicting reports as to their value in the prevention and treatment of the common cold.[1] Subsequent developments of the story include another popular article—this time in a widely read woman's magazine—which cannot but further the over-the-counter sale of these drugs, whose sales in 1950 have been estimated at over $100,000,000. However, the reports of further clinical controlled studies which have appeared in medical journals are in agreement as to the ineffectiveness of the antihistamines in the prevention and cure of colds. A further development is the reporting of serious toxic effects of these drugs in overdosage.

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The most interesting and perhaps the most important report[2] is the investigation by the Personnel of United States Naval Research Unit No. 4 at the Great Lakes Naval Training Station. Interestingly enough it was from this same station that the early favorable report originated.[3] Studies were made on recruits in barracks where groups of sixty men lived closely together with minimum outside contacts, and under close and constant medical care and supervision. During the two and one-half-month study period in the winter of 1950 there was a high incidence of acute respiratory disease, and an influenza epidemic due to type A prime influenza virus occurred. Three groups numbering approximately 350 each were studied. One group received an antihistamine, one a placebo, while the third was used as a control. No evidence was found that the antihistamines prevented or effected any important alteration in the symptomatology of influenza or infections corresponding to the common cold. Even when used in therapeutic dosage in another series they were found of no value. An attempt was made to study a "volunteer" group, similar to the one studied by Brewster at the station, where the sources of infection were not common. This study "did not permit of critical evaluation," but equally beneficial results were reported from placebos and the antihistaminic drugs.

Browning[4] has reported a study made on college freshmen living in dormitories at Oberlin, which extended over a period of thirty-one weeks. The differences occurring in three groups of approximately 100 each, one receiving an antihistamine, one a placebo, and the third used as a control, were statistically insignificant. Browning concludes that his study presented no evidence that the antihistamine used had any important effect in preventing or ameliorating colds observed among the subjects studied.

In both of these studies the subjects lived in close contact in dormitories, and hence the contacts in all three groups were common, a point

that was stressed in the August JOURNAL editorial as being of great importance in evaluating results. In light of the fact that there is no easy or certain way of defining or diagnosing the common cold, common contact is the only possible way of giving reasonable assurance that the same infection or infections are being studied in the histamine, placebo, and control groups.

The most recent report is a study by Lowell and his associates at Boston University[5] where the antihistamines were used for treatment over a period of three winter months. Three groups of about 180 each were given a different antihistamine, while a fourth group of similar size received a placebo. The authors were unable to distinguish any effect of the three drugs on the common cold that differed significantly from those receiving the placebo.

Another industrial report[6] is in line with previous industrial reports where the antihistamines have been extensively used in an attempt to reduce absenteeism due to colds. Baughn, Medical Director of a General Motors plant, dispensed 43,000 doses of seven different antihistamines over a period of eighteen months for "colds." Sixty-six per cent of 4,627 reported "perfect results." "Perfect" is not defined. Only 27 per cent of 1,336 "controls" given aspirin or an aspirin-phenacetin-caffeine remedy reported "perfect" results. Twenty-three per cent of those receiving the antihistamines reported side reactions. Baughn concludes that the use of antihistamines in the treatment of colds gave "excellent symptomatic results." Thompson, Medical Director of another General Motors plant, in his discussion of Baughn's paper presented figures to show that in his experience absenteeism was not lower in a group given antihistamines for colds. His conclusion is that unless there is a closer check on employees and their absenteeism, it will be difficult to arrive at any definite conclusion on the value of the antihistamines in industry.

SERIOUS TOXIC EFFECTS

While it is well known that the antihistamines in therapeutic doses may have unpleasant side effects, which seem to vary with the drug used and according to individual idiosyncrasy, it is not so generally recognized that serious toxic effects and even death may follow an overdose. Wyngaarden and Seevers[7] have recently collected the reports of eleven deaths from overdosage, including two previously unreported. *Eight of the eleven were in children from 6 months to 2 years of age.* In addition, they report on eighteen cases of nonfatal excessive ingestion which developed severe alarming symptoms. Seven of these were in children. While in adults excessive ingestion leads to depressant states, in children the predominating symptom of overdosage is convulsions. For example, they cite one 6-month-old child who died in convulsions two hours after the ingestion of an unknown amount of Benadryl, and another who died in a postconvulsive coma two and three-quarters hours after the ingestion of 600 mg. of Neo-Antergan. One death occurred in convulsions four hours after taking 1,400 mg. of pyranisamine hydrochloride, and another death in convulsions following the ingestion of 700(?) mg. of Dramamine. In two

of the fatal cases there was an hyperpyrexia of 107° F. Convulsions were also the outstanding symptom of most of the nonfatal cases following accidental poisoning in children. In discussing treatment they suggest the use of lavage and the avoidance of an emetic. They further suggest the use of short-acting barbiturates to control the convulsive states, so as not to add to the depressant state which may follow the convulsive state. The use of ether to control convulsions may be indicated and needs further evaluation. One of the cases they report is very instructive. A 6-month-old infant was seen by a physician soon after the consumption of an unknown amount of diphenhydramine. He found nothing seriously wrong and did not prescribe treatment. One hour later the child became violently ill and was rushed to the hospital in convulsions. Death occurred about two hours after the ingestion of the drug.

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Evidence is thus seen to be accumulating that the antihistaminic drugs are without value in the prophylaxis and treatment of that rather vague entity known as the common cold. We have no criticism of Brewster and the other earlier investigators whose early reports were more favorable. It is only the oft repeated story of a therapeutic suggestion, trial, and check. Our criticism is directed rather to the lay magazines which discussed publicly a suggested but unproved drug, and in particular to those pharmaceutical firms who blatantly advertised an unproved "cold cure" in the press and over the radio. Those who control the press and radio are not beyond censure.

So far as the pediatrician is concerned, the problem that has developed is chiefly one of poisoning resulting from the accidental ingestion of toxic doses of an over-the-counter "household remedy" which may terminate fatally. Few lay people can understand how a drug they can buy openly over the counter may be dangerous. Given a few more fatalities—and these are bound to occur as long as people are uninformed and careless, and children are children—it may be possible to put the antihistaminic drugs in the class where they belong as obtainable only on a physician's prescription. Certainly every effort should be made by the medical profession to make parents aware that the antihistamines are dangerous in overdosage, and that their accidental ingestion by young children may prove fatal.

B. S. V.

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